recorded weekly. Clinical laboratory determinations were performed after 13 weeks of treatment. Satellite animals were sampled for toxicokinetic evaluation at various time-points on Days 0 and 90. All animals that died during the study were necropsied. All surviving animals were sacrificed at the end of the treatment period. Selected organs were weighed. Organ/tissue samples were fixed and preserved at necropsy for all animals. Selected organs/tissues from all animals sacrificed at the end of the treatment period or sacrificed moribund were examined histopathologically.

CONCLUSION:

After dermal application of CD5789 cream, CD1 mice were exposed to CD5789 at all doses, with a systemic exposure that was similar between males and females and which increased with dose levels. Treatment-related effects occurred in the skin (inflammatory changes at the application sites, with hyperplasia, hyperkeratosis and parakeratosis, correlated with local reactions observed during in life part of the study), non-glandular stomach (minimal or slight hyperplasia/hyperkeratosis of the mucosa at the limiting ridge) and bone (minimal epiphyseal growth plate disorganisation in the femur and sternum), identified as main target organs. These effects occurred with a dose-response relationship. Other mild changes, most probably related to the inflammatory process in the treated skin, occurred in clinical chemistry and hematology parameters as well as in the lymph nodes, bone marrow and spleen.

Studies with the CD5789 cream formulation in minipigs

55. RDS.03.SRE.8677 - CD5789 Cream B 4-week topical (dermal application) administration toxicity study in the Göttingen minipig.

OBJECTIVE:

The objectives of the study were to assess the local tolerance and the systemic toxicity of CD5789 cream by daily dermal application to Göttingen minipigs for 4 weeks.

MATERIAL AND METHODS:

Males and females Göttingen minipigs (3 to 4 months old, four per group and per sex) were topically treated with CD5789 formulated in cream at 10 µg/g at a dosing volume of 1 or 2 mL/kg or 50 µg/g at a dosing volume of 2 mL/kg. Placebo was applied at a dosing volume of 2 mL/kg. Animals were dosed daily, 7 days a week, for approximately 2 consecutive weeks. The dosage form was spread over 2 application-sites to achieve a total percentage of body surface treated of approximately 10%. Treated areas were protected (non-occlusive) during approximately a 6-hour exposure period (or 24 hours during non-working days). Due to the severity of cutaneous reactions on treated area in all animals included in the study, the treatment was prematurely stopped after 2 weeks. Due to the premature stop of treatment, cardiovascular examination, ophthalmology, blood collection for toxicokinetic evaluation (multiple dosing), bioanalysis, blood and urine collections for clinical pathology investigations, necropsy, histotechnique and histopathological examination, initially scheduled at the end of the 4-week treatment period were not performed.

CONCLUSION:

Dermal application for approximately 2 consecutive weeks of CD5789 cream at 10 µg/g or 50 µg/g at dosing volumes of 1 or 2 mL/kg was not tolerated. On the treated areas, CD5789 cream at both concentrations and all volumes of administration induced dose-related severe cutaneous effects mainly consisting of erythema and/or edema, desquamation and crusts/scabs, leading to suspend treatment for all animals. Local irritation was also noted for all animals treated with the placebo cream. The dose volume of 1 or 2 mL/kg was considered too high for further dermal minipig studies to be conducted with the cream.

56. RDS.03.SRE.8684 - CD5789 Cream B 4-week topical (dermal application) administration toxicity study in the Göttingen minipig.

OBJECTIVE:

The objectives of the study were to assess the local tolerance and potential systemic toxicity of CD5789 cream at a concentration of 10 µg/g, when administered daily by dermal application, to male and female Göttingen□ minipig for 4 consecutive weeks.

MATERIAL AND METHODS:

The study was conducted using groups of 4 males and 4 females and according to the design presented in Table 6.

Table 6 Design of the 4-week topical administration toxicity study in the Gottingen® minipig (RDS.03.SRE.8684)

Group	Concentration of CD5789 in Drug Product (µg/g)	Dose-volume (mL/kg/day)	Dose levels CD5789 (mg/kg/day)	Quantity of CD5789 applied (µg/cm² approximately)***	Sites
Placebo control	0	0.125*	0	0	left flank
	0	0.375**	0	0	right flank
Low dose	10	0.25	0.0025	0.05	both flank
Mid dose	10	0.5	0.005	0.1	both flank
High dose	10	0.75	0.0075	0.15	both flank

The density was considered as equal to 1 for dose calculation.
* Corresponding to the volume applied on each flank in the low dose group
** Corresponding to the volume applied on each flank in the high dose group
*** Estimation based on 10% of body surface treated, which represents approximately 400 cm^2 for an average bodyweight of 8kg

The formulations were applied over two application-sites (one on each flank, avoiding the spinal column) to achieve a treated area of approximately 10% of body surface area. Treated areas were protected for 6 hours (or 24 hours during non-working days). After the exposure period, cutaneous reactions at the application-sites were evaluated and application-sites rinsed. Parameters examined included daily morbidity/mortality checks, clinical observations, food consumption estimate, and weekly individual body weight recording. Cardiovascular, ophthalmological examinations and clinical pathology investigations were performed during predosing and during week 4. All animals were sampled for toxicokinetic evaluation on the first day and after 28 days of treatment. The LOQ of the bioanalytical method (LC-MS/MS) was 0.05 ng/mL. At the end of the dosing period, necropsy examinations were performed, organ weights were recorded and selected tissues were microscopically examined.

CONCLUSION:

The skin was the only target organ. CD5789 cream at 10 µg/g was not tolerated when applied at dosing volumes of 0.5 and 0.75 mL/kg/day (corresponding to an application of 0.1 and 0.15 µg/cm2/day of active ingredient, respectively).

57. RDS.03.SRE.12851 - CD5789 Cream (cream b) 4-week topical (dermal application) tolerance study in the Göttingen minipig.

OBJECTIVE:

The objectives of this study were to assess the local tolerance of CD5789 cream in Göttingen□ minipigs for four consecutive weeks at different dose volumes.

MATERIAL AND METHODS:

The study was conducted according to the design presented in Table 7.

Table 7 **Design of the 4-week topical tolerance study in the Göttingen® minipig (RDS.03.SRE.12851)**

Group	Application site	Treatment	Concentration of CD5789 in formulation % (µg/g)	Dose Volume (mL) per flank*	Estimated dose CD5789 applied (µg/cm²)**
1	Left flank	Placebo	0	0.5	
	Right flank	CD5789 cream	0.005% (50)	0.5	0.1
2	Left flank	Placebo	0	1.25	
	Right flank	CD5789 cream	0.005% (50)	1.25	0.25
3	Left flank	Placebo	0	2.5	
	Right flank	CD5789 cream	0.005% (50)	2.5	0.5
4	Left flank	Placebo	0	0.5	
	Right flank	CD5789 cream	0.01% (100)	0.5	0.2

*: for 10 kg body weight.
**: theoretical value considering an area of 250 cm² per flank.

Animals (3 females per group) were treated for four consecutive weeks for approximately 6 hours per day. The test item or placebo cream were applied on clipped areas (the left flank for the placebo and right flank for the test item), both flanks representing a total of 10 % of the whole body area, and were held in contact with the skin with a non-occlusive dressing. The treated areas were then rinsed with lukewarm water. The following were assessed: morbidity/mortality, clinical observations (including rectal temperature on some occasions), local tolerance, bodyweight and food consumption. All animals were necropsied at the end of the treatment period and examined for macroscopic lesions. Histopathological evaluation was performed on treated and untreated skin from all animals.

CONCLUSION:

Daily dermal application of CD5789 cream for four weeks in the Göttingen minipig at concentrations of 0.01 % and 0.005 % in dose volumes calculated on the basis of 0.05 to 0.25 mL/kg/day respectively, induced a dose-related irritation reaction (erythema) at the application sites, with a maximum severity and incidence after 3 weeks of treatment. The concentration of 0.005 % under an application volume calculated on the basis of 0.05 or 0.125 mL/kg/day induced less marked local reactions. At the microscopic examination, slight histological changes related to irritation were observed without a clear dose-response relationship. Local reactions tended to decrease at the end of the treatment period.

58. RDS.03.SRE.12852 - CD5789 Cream 13-week topical (dermal application) toxicity study in the Göttingen® minipig.

OBJECTIVE:

The objectives of the study were to assess the local tolerance and systemic toxicity of CD5789 cream applied daily to the skin of male and female Göttingen minipigs for 13 weeks and to determine the concentrations of CD5789 in plasma samples under the defined experimental conditions.

MATERIAL AND METHODS:

CD5789 formulated in cream at 10µg/g (2.5 µg/kg/day CD5789), 50µg/g (12.5 µg/kg/day CD5789) and 100µg/g (25 µg/kg/day CD5789) was administered daily by dermal application to male and female Göttingen minipigs for 13 consecutive weeks, according to the following design:

Group/ Treatment	Treatment	Concentration of CD5789 (in %, w/w)	Volume administered (mL/kg/day)	Dose level [a] (µg CD5789/cm²/ day)	Dose level (µg/kg/day)	Number of animals	
						Males	Females
1. Control	Placebo	0	0.25	0	0	4	4
2. Low dose	Test item	0.001	0.25	0.05	2.5	4	4
3. Mid dose	Test item	0.005	0.25	0.25	12.5	4	4
4. High dose	Test item	0.01	0.25	0.5	25	4	4 + 1 [b]

[a]: Calculated for a 10 kg minipig and a treated area of 500 cm² (approximately 10 % of total body surface).
[b]: Female no. 630 with outlier exacerbated local reactions was replaced by spare female no. 633, on study day 21.

Group 1 animals (control) received the placebo (CD5789 placebo cream). Animals were treated for 13 consecutive weeks and were topically exposed to the test item for approximately 6 hours per day. Formulations were applied on clipped areas (back and sides of the trunk) representing 10% of the whole body area and held in contact with the skin with a non-occlusive dressing for 6 hours. The treated area was then rinsed with lukewarm water. The following parameters were assessed: morbidity/mortality, clinical observations, local tolerance, ophthalmology, body weight, food consumption, cardiovascular examinations, hematology, coagulation, serum clinical chemistry, urinalysis, levels of CD5789 in plasma at the end of treatment period, (using a validated LC-MS/MS method with a Limit of Quantification of 0.05 ng/mL). All animals were necropsied at the end of the treatment period and examined for macroscopic lesions. Selected organs were weighed. Histopathological evaluation was performed on selected tissues and organs.

CONCLUSION:

Topical application of CD5789 at 10µg/g and 50µg/g at the dosing volume of 0.25 mL/kg/day was tolerated in minipigs for 13 consecutive weeks. Topical application of CD5789 100µg/g cream induced marked skin reactions, leading to the interruption of treatment for one animal. CD5789 100µg/g cream applications was considered to exceed the maximal local tolerated dose.

59. RDS.03.SRE.12875 - CD5789 Cream 9-month topical (dermal application) toxicity study in the

OBJECTIVE:

The objectives of the study were to assess the local tolerance and potential systemic toxicity of CD5789 formulated in cream at 0.001% (2.5 µg/kg/day CD5789), 0.005% (12.5 µg/kg/day CD5789) and 0.01% (25 µg/kg/day CD5789) when administered daily at 0.25 mL/kg/day by dermal application to male and female Göttingen minipigs for at least 39 consecutive weeks, to determine the concentration of CD5789 in plasma samples.

MATERIAL AND METHODS:

The study was conducted according to the following design:

Group/ Treatment	Concentration of formulation (in%, w/w)	Volume administered (mL/kg/day)	Dose level * (µg CD5789 /cm²/day)	Dose level ** (µg/kg/day)	Number of animals for necropsy at			
					Terminal sacrifice Week 40 (1)		Recovery Week 44 (2)	
					M	F	M	F
1. Placebo	0	0.25	0	0	4	4	2	2
2. Low dose	0.001	0.25	0.05	2.5	4	4	/	/
3.Mid dose	0.005	0.25	0.25	12.5	4	4	/	/
4. High dose	0.01	0.25	0.50	25	4	4	2	2

M: males, F: females
1): Scheduled to be sacrificed at the end of the treatment period.
2): Sacrificed at the end of the treatment-free period.
/: not applicable.
*: Calculated for a 10 kg minipigs and a treated area of 500 cm^2 (approximately 10% of total body surface area)
**: Density of formulations considered as 1 (quantity of formulation applied: 0.25 g/kg/day)
Group 1 animals (control) received the placebo (CD5789 placebo cream)

Animals were treated for 39 consecutive weeks followed by a 4-week treatment-free period. Animals were topically exposed to the test item or placebo for approximately 6 hours per day, 7 days per week. Formulations were applied on clipped areas (back and sides of the trunk, avoiding the spinal column area), representing 10% of the whole body surface area and held in contact with the skin with a non-occlusive dressing for 6 hours. The treated area was then rinsed with lukewarm water. The following parameters were assessed: morbidity/mortality, clinical observations, local tolerance, ophthalmology, body weight, food consumption, cardiovascular examinations, hematology, coagulation, serum clinical chemistry, urinalysis, levels of CD5789 in plasma at the beginning and at the end of the treatment period (using a validated LC-MS/MS method with a limit of quantification of 0.05 ng/mL). Any animals found dead or sacrificed moribund were necropsied. All surviving animals were necropsied at the

end of the treatment period or treatment-free period and examined for microscopic lesions. Selected organs were weighed. Histopathological evaluation was performed on selected tissues and organs.

CONCLUSION:

After topical application of CD5789 cream at 0.001%, 0.005% and 0.01% at the dosing volume of 0.25 mL/kg/day in minipigs for 39 consecutive weeks, CD5789 plasma concentrations were very low and quantifiable at the two highest doses only, with individual concentrations ranging from 0.0501 to 0.307 ng/mL, whatever the dose applied. The treatment was well tolerated and did not result in any systemic adverse effect. Only local reactions occurred at the treatment site, which mainly consisted of erythema with associated minimal to slight histological findings. Local reactions were more marked during the first month of dosing and completely resolved after the 4-week treatment-free period. They remained within the expected range of local reactions following topical application of a retinoic acid receptor-agonist.

Repeated oral dose toxicity studies

Repeated oral dose toxicity in rats

60. RDS.03.SRE.8549 - CD5789 and CD5960 2-week oral toxicity study in the Sprague Dawley rat.

OBJECTIVE:

The objectives of the study were to determine the potential toxic effects of CD5789 and CD5960 in the Sprague Dawley rat following daily oral gavage for 2 weeks. Only results related to CD5789 administration are presented thereafter.

MATERIAL AND METHODS:

CD5789 was administered daily by gavage to 5 Sprague-Dawley rats/sex/group at dose-levels of 0 (vehicle), 0.1, 1, 5 or 10 mg/kg/day for 2 weeks. Animals were observed daily for mortality and clinical signs. Body weights and food consumptions were recorded weekly. Blood was sampled at selected time points (1, 2, 4, 8 and 24 hours post-dosing) on day 14 for proof of exposure evaluation of CD5789. At the end of the treatment period, animals were necropsied and selected organs and tissues were sampled for weighing and for microscopic examination.

CONCLUSION:

Oral administration (gavage) of CD5789 to Sprague-Dawley rats at 5 and 10 mg/kg/day was not tolerated and resulted in major clinical signs and/or the premature death of most animals before the end of the 2-week treatment period. A gender difference due to higher exposure of females was noted for CD5789.

The NOEL was established at 0.1 mg/kg/day for females and 1 mg/kg/day for males, respectively. These doses corresponded to a plasma Cmax value of 10.4 and 4.2 ng/mL for females and males, respectively.

61. RDS.03.SRE.8594 - CD5789 4-week oral (gavage) administration toxicity study in the Wistar rat.

OBJECTIVE:

The objective of this study was to assess the systemic toxicity and toxicokinetic parameters of CD5789 in male and female Wistar rats upon repeated oral administration during 4 consecutive weeks.

MATERIAL AND METHODS:

Ten Wistar rats/sex/group were treated by gavage with CD5789 at 0 (vehicle) 0.05, 0.1, 0.5 or 1 mg/kg/day at 2 mL/kg, for 4 consecutive weeks. Control animals were treated with the vehicle alone (0.5% CMC - 0.1% Tween 80 in purified water). Animals

were regularly monitored for clinical signs, body weight and food consumption. Ophthalmologic examinations were performed on all animals during the pre-dosing period and on all animals of the placebo and high-dosage groups at the end of the dosing period. At the end of the 4-week treatment period, hematology, coagulation and serum chemistry parameters were analyzed and urinalysis was performed. At the end of the study all animals were sacrificed and underwent necropsy. Selected organs were weighed and subjected to histopathological evaluation.

Additional satellite animals (6/sex in treated groups and 2/sex in the control groups) were used for plasma drug level and toxicokinetic evaluation on Days 1 and 22. The corresponding plasma samples were analyzed by HPLC with ESI-MS/MS detection (LLOQ: 0.25 ng/mL).

CONCLUSION:

The skin, spleen, bone and stomach were identified as target organs. Treatment-related effects occurred at a lower dose level in females, consistent with a gender related difference in systemic drug exposure. The NOAEL was set at 0.5 mg/kg/day for males and 0.1 mg/kg/day for females. The systemic exposure to the parent compound at these dose levels (AUC0-24h at Day 22) was 105.09 ng.h/mL in males and 100.19 ng.h/mL, in females.

62. RDS.03.SRE.12650 - CD5789 13-week oral (gavage) toxicity study in the Wistar rat followed by a 4-week recovery period.

OBJECTIVE:

The objectives of the study were to determine the toxicity and systemic exposure of CD5789 following daily oral (gavage) administration to the male and female Wistar rat for 13 consecutive weeks and to assess reversibility of effects at the high dose during a recovery period of 4 weeks following the end of dosing.

MATERIAL AND METHODS:

The study was conducted according to the following design:

Group Treatment	Dose level (mg/kg/day)		Dose volume (mL/kg/day)	Dose concentration (mL/kg/day)		Number of animals			
						Terminal sacrifice[a]		Recovery[b]	
	Male	Female		Male	Female	Male	Female	Male	Female
1. Control	0	0	2	0	0	10 (3)	10 (3)	6	6
2. Low Dose	0.1	0.05	2	0.05	0.025	10 (6)	10 (6)	-	-
3. Intermediate Dose	0.5	0.1	2	0.25	0.05	10 (6)	10 (6)	-	-
4. High Dose	0.75	0.2	2	0.375	0.1	10 (6)	10 (6)	6	6

[a] sacrificed at the end of the treatment period (Day 91/92).
[b] sacrificed at the end of the treatment-free period (Day 119).
Satellite animals for toxicokinetics are indicated in brackets. These animals were sacrificed and discarded without necropsy after the last blood sampling occasion.
M: male.
F: female.
-: not applicable.

Group 1 animals (control) received the vehicle (0.5 % carboxymethylcellulose and 0.1 % Tween 80 in water for injection). Mortality, clinical signs, body weight and food consumption were recorded for all animals during the pre-dosing, dosing and recovery periods. Ophthalmologic examinations were performed on all animals during the pre-dosing period and on all animals of the placebo and high-dosage groups at the end of the dosing period. Clinical laboratory determinations were performed after 13 weeks of treatment and at the end of the treatment-free period. Satellite animals were sampled for toxicokinetic evaluations at various time-points after dosing on Days 0 and 87. All animals were sacrificed at the end of the treatment period or after a treatment-free period of 4 weeks. Selected organs were weighed. Organ/tissue samples were fixed and preserved at necropsy for all animals. Selected organs/tissues from group 1 and 4

animals sacrificed at the end of the treatment and treatment-free periods underwent histopathology.

CONCLUSION:

The NOAEL was established at 0.50 mg/kg/day in males and 0.10 mg/kg/day in females based on the growth plate disorganization in the stifle joint noted at the high dose in males (0.75 mg/kg/day) and in females (0.20 mg/kg/day). Minor findings in the skin, forestomach and spleen were not considered to be adverse. The dose of 0.50 or 0.10 mg/kg/day CD5789 in males or females, respectively, corresponded to a systemic exposure (AUC0-24h) of 130 ng.h/mL in males and 96.0 ng.h/mL in females at the steady state (Day 87).

63. RDS.03.SRE.12863 - CD5789 26-week oral (gavage) toxicity study in the Wistar rat followed by a 6-week treatment-free period.

OBJECTIVE:

The objectives of the study were to determine the toxicity of the test item CD5789 following daily oral (gavage) administration in the Wistar rat for 26 consecutive weeks, to evaluate the possible regression of any toxic signs during a 6-week treatment-free period and to assess systemic exposure under the defined experimental conditions.

MATERIAL AND METHODS:

The study was conducted according to the following design:

Group/Treatment	Dose level (mg/kg/day)		Dose volume (mL/kg/day)	Dose concentration (mg/mL)		Number of animals			
						Terminal sacrifice [a]		Recovery [b]	
	Males	Females		Males	Females	Males	Females	Males	Females
1. Control	0	0	2	0	0	15 (3)	15 (3)	10	10
2. Low dose	0.1	0.05	2	0.05	0.025	15 (6)	15 (6)	/	/
3. Intermediate dose	0.5	0.2	2	0.25	0.1	15 (6)	15 (6)	/	/
4. High dose	1.25	0.5	2	0.625	0.25	15 (6)	15 (6)	10	10

[a]: sacrificed at the end of the treatment period.
[b]: sacrificed at the end of the treatment-free period.
Satellite animals for toxicokinetics are indicated in brackets.
/: not applicable.

Group 1 animals (control) received the vehicle [0.5 % (w/v) carboxymethyl cellulose and 0.1% (w/v) Tween 80 in water for injection].

Morbidity/mortality checks were performed at least twice daily. Clinical observations were performed daily. A full clinical examination was performed weekly. Ophthalmological examinations were performed during pretest and at the end of the study. Individual body weights were recorded weekly. Food consumption was measured weekly for each cage of animals. Clinical laboratory determinations were performed on Days 91/92 and 182/183 (weeks 14 and 27, respectively) and at the end of the treatment-free period (Day 224). Satellite animals were sampled for toxicokinetic evaluations at various time-points after dosing on Days 0 and 168. One high dose female sacrificed for ethical reasons was necropsied. All surviving animals were sacrificed at the end of the treatment period or after a treatment-free period of 6 weeks and necropsied. Selected organs were weighed. Organ/tissue samples were fixed and preserved at necropsy for all animals. Selected organs/tissues from animals sacrificed at the end of the treatment or treatment-free periods and from the female sacrificed for ethical reasons were examined histopathologically.

CONCLUSION:

The daily oral gavage in the Wistar rat of CD5789 for 26 weeks was clinically well tolerated at doses of up to 0.5 mg/kg/day in males and 0.2 mg/kg/day in females, with no adverse findings at histopathology. At the highest doses of 1.25 mg/kg/day (males)

and 0.5 mg/kg/day (females), a lower food consumption and a lower body weight gain, and histological changes in the femoral and/or tibial stifle joints, stomach and skin were recorded. The persistence of the histological findings in the femur and/or tibia at 0.5 mg/kg/day in the females and to a lower extent at 1.25 mg/kg/day in the males and the persistence of the effect on the body weight was considered as adverse. The NOAEL was established at 0.5 mg/kg/day in the males and 0.2 mg/kg/day in the females. These doses correspond to an AUC0-24h at steady state (Day 168) of 63.7 ng.h/mL in males and 199 ng.h/mL in females.

Repeated oral dose toxicity in dogs

64. RDS.03.SRE.12599 - CD 5789 Single dose comparative pharmacokinetic study by the oral (gavage) or intravenous (bolus injection) routes followed by a 14-day oral (gavage) dose-range finding toxicity study in the beagle dog.

OBJECTIVE:

The objectives of the study were to evaluate CD5789 overall tolerance in the Beagle dog when administered daily by oral administration (gavage) for 14 days, allowing to select dose levels for a subsequent toxicity study. The pharmacokinetic profiles of CD5789 after a single intravenous or oral administration are described in Section 3. Pharmacokinetics, 2) Absorption.

MATERIAL AND METHODS:

One dog/sex/group received 0 (vehicle), 0.1, 0.5, 1, 2.5 mg/kg/day CD5789 formulated in 0.5 % (w/v) CMC and 0.1 % Tween 80 in water for injection for 14 days. Morbidity/mortality checks were performed at least twice daily. Clinical observations were performed daily. More detailed examinations (including rectal temperature and behavioral assessment on some occasions) were performed at pretest for all animals, during the first week of treatment and at termination. Body weight was recorded weekly during the acclimatization period, then twice weekly (including day 0) during the treatment period and food consumption was measured daily for each animal. Clinical laboratory determinations were performed pretest for all animals and on day 13 for surviving animals. A clinical laboratory determination was performed on day 10 for one female sacrificed for ethical reasons. Blood sampling for toxicokinetic evaluation was performed on Day 0 and Day 13. Additional blood sampling for toxicokinetic evaluation was performed from animals sacrificed for ethical reasons on Days 8 and 10. Animals sacrificed for ethical reasons during the study underwent necroscopy. All surviving animals were sacrificed the day after the last day of treatment (Day 14). Selected organs were weighed. Organ/tissue samples were fixed and preserved at necropsy for all animals. Histopathology was performed for selected organs/tissues from all animals.

CONCLUSION:

CD5789 administered once daily by the oral route to beagle dogs for 14 days at the dose levels of 0.5, 1 and 2.5 mg/kg/day induced dose related severe clinical signs with body weight loss for females treated at 0.5 and 2.5 mg/kg/day and histopathological changes from 0.5 mg/kg/day.

Based on these observations, the Maximal Tolerated Dose (MTD) was considered below the dose level of 0.5 mg/kg/day. Conversely, daily administration of CD5789 at 0.1 mg/kg/day resulted in a minimal adrenal histopathological change in the female.

65. RDS.03.SRE.12601 - CD 5789 4-week oral (gavage) toxicity study in the beagle dog.

OBJECTIVE:

The objectives of the study were to determine the oral toxicity of CD5789 to Beagle dog for 4 consecutive weeks and to assess systemic exposure under the defined experimental conditions.

MATERIAL AND METHODS:

Three Beagle dogs/sex/group received CD5789 formulated in 0.5 % (w/v) CMC and 0.1 % Tween 80 in water for injection at 0 (vehicle), 0.03, 0.08 or 0.2 mg/kg/day for 4 weeks. Group 1 animals (control) received the vehicle (0.5 % (w/v) CMC and 0.1 % Tween 80 in water for injection). Morbidity/mortality checks were performed at least twice daily. Clinical observations were performed daily. More detailed examinations (including behavioral assessment and rectal temperature) were performed at pretest and once weekly. Ophthalmological examination was performed at pretest and on Day 22. Body weight was recorded weekly for each animal. Food consumption was measured daily for each animal. Cardiovascular examinations were performed at pretest and on Days 1 and 23. Clinical laboratory determinations were performed pretest and on Day 24. Blood sampling for toxicokinetic evaluations was performed on Days 0 and 24 at various time-points. One male treated at 0.2 mg/kg/day was sacrificed for ethical reasons during the study (Day 16) and underwent necroscopy. All surviving animals were sacrificed after 4 weeks of treatment. Designated organs were weighed. Selected organ/tissue samples taken at necropsy were fixed and preserved for all animals. Histopathological examinations were performed for all organs/tissues from all animals in groups 1 (control) and 4 (high dose) and for the skin, liver, adrenal glands and bone (femur and sternum) from all animals in the low and intermediate groups.

CONCLUSION:

Daily gavage administration of CD5789 to the Beagle dog at 0.08 or 0.2 mg/kg/day for 4 weeks induced dose-related clinical signs (skin changes, ear, and eye secretions). These clinical signs are part of the known treatment-related effects of retinoid compounds in the dog and were correlated with hematological, clinical pathology and histopathology findings at 0.2 mg/kg/day.

Changes for animals treated at 0.08 mg/kg/day were noted with a minor severity and/or incidence. At 0.03 mg/kg/day, only colored skin was sporadically observed during the first week of treatment and no clinical pathology or histopathological changes were noted.

The No Observed Adverse Effect Level (NOAEL) was established at 0.03 mg/kg/day corresponding to AUC0-24h of 124 ng.h/mL in males and 177 ng.h/mL in females, at the end of the treatment period.

66. RDS.03.SRE.12672 - CD5789 13-week oral (gavage) toxicity study in the Beagle dog followed by a 4-week recovery period.

OBJECTIVE:

The objectives of the study were to assess the toxicity and systemic exposures of CD5789 in Beagle dogs after repeated daily oral (gavage) administration for 13 consecutive weeks and to assess the reversibility of any effects after a recovery period of 4 weeks.

MATERIAL AND METHODS:

CD5789 at 0 (vehicle: 0.5 % (w/v) CMC and 0.1 % Tween 80 in water for injection), 0.02, 0.045, and 0.09 mg/kg/day was administered by gavage to 4 Beagle dogs/sex/group for 13 consecutive weeks. Two additional dogs/sex were added in the control and high dose group to assess the reversibility of any effects after a recovery period of 4 weeks.

Morbidity/mortality checks were performed at least twice daily. Clinical observations were performed daily. More detailed examinations (including rectal temperature and behavioral assessment on some occasions) were performed at pretest, at least once

monthly during the treatment period and at each termination. Ophthalmologic examinations were performed at pretest, during Week 13 and the last week of the recovery period. Body weight was recorded every week for each animal. Food consumption was measured daily for each animal. Cardiovascular examinations were performed at pretest and during Weeks 1 and 13. Clinical laboratory determinations were performed at pretest and during Weeks 5, 13 and at the end of the recovery period. Blood sampling for toxicokinetic evaluations were performed at various time points during Weeks 1, 6 and 13. All animals were sacrificed at the end of the treatment period or after a 4-week treatment-free period and underwent necropsy. Designated organs were weighed. Organ/tissue samples were fixed and preserved at necropsy for all animals. Selected organs/tissues from all animals underwent histopathology.

CONCLUSION:

Daily oral (gavage) administration to Beagle dog of CD5789 at doses up to 0.09 mg/kg/day for 13 weeks was well tolerated, including only slight transient clinical signs (skin changes, hypersalivation) during the first 4 weeks of treatment and minimal histopathological cutaneous changes at 0.045 and 0.09 mg/kg/day. Changes were minimal with a low severity, incidence and distribution and did not correlate with hematology or clinical pathology findings. The reversible skin changes are part of the known treatment-related effects of retinoid compounds in dogs or may be seen spontaneously with this minimal level of severity. The No Observed Adverse Effect Level (NOAEL) was established at 0.09 mg/kg/day. The corresponding systemic exposure (AUC0-24h) after 91 days of treatment was 213 and 250 ng.h/mL in males and females, respectively.

67. RDS.03.SRE.12864 - CD5789 39-week oral (gavage) toxicity study in the beagle dog followed by an 8-week treatment-free period.

OBJECTIVE:

The objectives of the study were to determine the toxicity of the test item CD5789 following daily oral (gavage) administration to beagle dogs for 39 weeks, to evaluate the possible regression of any toxic signs during an 8-week treatment-free period and to assess systemic exposure under the defined experimental conditions.

MATERIAL AND METHODS:

The study was conducted according to the following design:

Group/Treatment	Dose level (mg/kg/day)	Dose volume (mL/kg/day)	Dose concentration (mg/mL)	Number of animals:			
				Terminal sacrifice [a]		Recovery [b]	
				Males	Females	Males	Females
1. Control	0	2	0	4	4	2	2
2. Low dose	0.02	2	0.01	4	4	/	/
3. Intermediate dose	0.06	2	0.03	4	4	/	/
4. High dose	0.18	2	0.09	4	4	2	2

[a]: sacrificed the end of the treatment period.
[b]: sacrificed at the end of the treatment-free period.
/: not applicable.

Group 1 animals (control) received the vehicle [0.5 % (w/v) carboxymethyl cellulose (300-600 centipoises at 2 %) and 0.1 % (w/v) Tween 80 in water for injection]. Morbidity/mortality checks were performed at least twice daily. Clinical observations were performed daily. More detailed examinations (including behavioral assessment and rectal temperature measurement on some occasions) were performed before the initiation of treatment, weekly for the first four weeks of treatment and then at least once monthly the remainder of the treatment period and during the treatment-free period. Ophthalmological examination was performed pre-test and during Weeks 13/14 and 39. Body weight was recorded weekly and food consumption daily. Cardiovascular examinations, including ECG analysis, were performed pre-test, on Day 1 and during Weeks 13 and 39. Blood sampling and urine collection for clinical laboratory determinations were performed pre-test and during Weeks 13/14, 39 and 47.

	Blood sampling for toxicokinetic evaluations was performed at various time-points after dosing on Day 0 and during Weeks 14 and 39. Plasma concentrations of CD5789 were determined by a validated HPLC method with TIS-MS/MS detection with a limit of quantification of 0.5 ng/mL. All animals were sacrificed at the end of the treatment or treatment-free periods (Weeks 39 or 47) and underwent necropsied. Selected organs were weighed. Selected organs/tissues from all animals were examined histopathologically. CONCLUSION: After the daily oral administration of CD5789 to Beagle dogs for 39 weeks at doses of 0.02, 0.06 and 0.18 mg/kg/day, CD5789 was detected in the plasma of all animals. The mean systemic exposure at the end of the treatment period ranged from 124 to 434 ng.h/mL in males, 166 to 533 ng.h/mL in females. Expected effects, consistent with the pharmacological activity of CD5789, occurred in the skin and mucous membranes at all dose levels. These effects were fully reversible at 0.18 mg/kg/day. Dose levels of 0.06 and 0.18 mg/kg/day induced a decrease in mean body weight gain, associated to reduced food consumption, relative to controls. This effect on body weight gain was reversible at 0.18 mg/kg /day in males but not in females. In some treated males, a slight increase in the number of degenerate germ cells occurred in the testes, compared to background control. This change was not fully reversible since one male at 0.18 mg/kg/day still had minimally increased degenerate germ cells at the end of recovery. Due to these findings, a No Observable Adverse Effect Level (NOAEL) could not be determined. At the lowest dose of 0.02 mg/kg/day, the mean systemic exposure at the end of treatment was 124 ng.h/mL in males and 166 ng.h/mL in females. Although the study report concluded that a NOAEL could not be determined, the Applicant considers that effects observed at 0.02 mg/kg/day in females were not adverse due to their minimal severity.
3) genotoxicity: in vitro	**68. RDS.03.SRE.12526 - CD5789: Reverse Mutation in five Histidine-requiring strains of Salmonella typhimurium.** OBJECTIVE: The objective of the study was to assay CD5789 for its mutation potential in the reverse bacterial mutation assay (Ames test). MATERIAL AND METHODS: CD5789 was assayed for its mutation potential in 2 separate experiments in 5 histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of *Salmonella typhimurium*, both in the absence and in the presence of metabolic activation by an Aroclor 1254-induced rat liver post-mitochondrial fraction (S-9). An initial toxicity range-finder experiment (experiment 1) was performed following the plate incorporation methodology treatments in the absence and in the presence of S-9 in strain TA100 only, using final concentrations of CD5789 at 1.6, 8, 40, 200, 1000 and 5000 µg/plate, plus negative (vehicle) and positive controls. Following these treatments, no clear evidence of toxicity was observed. However, precipitation of CD5789 was observed on all plates treated at 1000 µg/plate and above. These data were considered acceptable for the mutation assessment and are provided as the Experiment 1 data for strain TA100. Plate incorporation methodology treatments of the remaining test strains were performed in the absence and in the presence of S-9 in Experiment 1 and used the same test concentrations employed for the range-finder experiment. Following these treatments, there was no clear evidence of toxicity, although reductions in revertant numbers with 5000 µg/plate treatments of strain TA102 in the absence and presence of S-9 may have been the result of toxicity. Precipitation of the test article was observed in all strains at 1000 µg/plate and above in the absence and presence of S-9.

Experiment 2 treatments of all tested strains were performed in the absence and in the presence of S-9 at concentrations up to either an estimate of the solubility limit in the assay system, or in the case of the strain TA102, up to possible toxic levels. In each case, narrowed concentration intervals were used to comprise the remaining test concentrations (concentration ranges of 31.25 to 1000 µg/plate employed for strains TA98, TA100, TA1535 and TA1537 and 62.5 to 2000 µg/plate for strain TA102) in order to investigate more closely those concentrations of CD5789 approaching the limit concentration levels, and considered most likely to provide evidence of any mutagenic activity. Plate incorporation methodology treatments were employed in the absence of S-9, but all treatments in the presence of S-9 were further modified in including a pre-incubation step. This was to intend increasing the range of mutagenic chemicals that could be detected using this assay system. Following these treatments there was no evidence of toxicity in any of the tested strains. However, several possible toxic effects were observed with the higher treatment concentrations of strain TA102 in the absence of S-9 only. Precipitation of CD5789 was observed in all strains at 500 µg/plate and above in the absence and presence of S-9.

CONCLUSION:

CD5789 did not induce mutation in 5 histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of *Salmonella typhimurium* when tested under the conditions of this study. These conditions included treatments at concentrations up to precipitating concentrations in the absence and in the presence of a rat liver metabolic activation system (S-9).

69. RDS.03.SRE.12525 - CD5789 Reverse Mutation in five Histidine-requiring Strains of Salmonella typhimurium, in the Presence of Ultra Violet light.

OBJECTIVE:

The objective of the study was to assay CD5789 for its photomutagenicity potential in the reverse bacterial mutation assay in combination with doses of UV light.

MATERIAL AND METHODS:

The photomutagenicity potential of CD5789 was assayed in 5 histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of *Salmonella typhimurium*, following exposure to a range of doses of UV light. Treatments were performed up to a maximum concentration of CD5789 of 1581 µg/plate to ensure that at least one precipitating treatment concentration was obtained, without performing a separate range-finder experiment.

Photomutation treatments of all the tested strains were performed using half-log treatment concentration multiples, to provide final concentrations of CD5789 at 5, 15.81, 50, 158.1, 500 and 1581 µg/plate, plus negative (vehicle) and positive controls as well as photopositive control treatments in strains TA1537 and TA102. This treatment concentration range was selected to thoroughly investigate a wide range of concentrations of CD5789, ensuring that UV light exposure of the test cells occurred for at least some of the test concentrations, whether or not any UV light blocking effects of the test article occurred. As no range-finder experiment or phototoxicity assessments were conducted, treatments in the photomutation experiment were performed using 2 UV light irradiation levels appropriate for each strain, together with unirradiated treatments. This was to ensure that appropriate combinations of chemical and UV light irradiation levels were available to allow for thorough investigation of photomutagenicity, whether or not any phototoxic effects might have occurred in this experimentation.

Plates treated with each strain were exposed to UVA light exposures of 5 and 10 mJ/cm2 for strain TA98, 2 and 4 mJ/ cm2 for strain TA100, 6 and 12 mJ/ cm2 for strain TA1535, 8 and 16 mJ/ cm2 for strain TA1537 and 60 and 120 mJ/ cm2 for strain TA102.

CONCLUSION:

CD5789 did not induce mutation in 5 strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537 and TA102), when treated at concentrations up to 1581 µg/plate (a precipitating concentration) at 2 separate UV light exposure levels appropriate for each strain.

70. RDS.03.SRE.12523 - CD5789 Mutation at the Thymidine Kinase (tk) Locus of Mouse Lymphoma L5178Y Cells (MLA) using the Microtitre^R Fluctuation Technique.

OBJECTIVE:

The objective of the study was to assay CD5789 for its genotoxicity to mammalian cell in the mouse lymphoma assay.

MATERIAL AND METHODS:

CD5789 was assayed for its ability to induce mutation at the tk locus (5-trifluorothymidine resistance) in mouse lymphoma cells using a fluctuation protocol. A 3-hour treatment incubation period was used for all experiments performed in the presence of S-9. In the absence of S-9, the range-finder was performed using 3 and 24 hour treatment incubation periods, Experiment 1 was performed using a 3 hour treatment incubation and Experiment 2 was performed using a 24 hour treatment incubation. In the cytotoxicity range-finding experiment, 3 hours treatment, 6 concentrations were tested, in the absence and presence of S-9, ranging from 25 to 800 µg/mL (limited by solubility in culture medium). The highest concentration of 25µg/mL, where reasonable cell growth was observed, yielded 9% and 16% RTG in the absence and presence of S-9, respectively. In the cytotoxicity range-finding experiment, 24 hours treatment, 9 concentrations were tested in the absence of S-9, ranging from 3.125 to 800 µg/mL (limited by solubility in culture medium). The highest concentration to give > 10% RTG, 12.5 □g/mL, yielded 62% RTG.

CONCLUSION:

CD5789 did not induce mutation at the tk locus of L5178Y mouse lymphoma cells when tested under the conditions employed in this study. These conditions included treatments up to toxic concentrations in 2 independent experiments in the absence and presence of a rat liver metabolic activation system (S-9).

71. RDS.03.SRE.12522 - CD5789 Induction of micronuclei in cultured human peripheral blood lymphocytes.

OBJECTIVE:

The objective of the study was to assay CD5789 for its genotoxicity in an *in vitro* micronucleus assay.

MATERIAL AND METHODS:

CD5789 was tested in an *in vitro* micronucleus assay using duplicate human lymphocyte cultures prepared from the pooled blood of 2 male donors in 2 independent experiments. Treatments covering a broad range of concentrations, separated by narrow intervals, were performed both in the absence and presence of metabolic activation (S-9). CD5789 was formulated in sterile anhydrous analytical grade dimethyl sulphoxide (DMSO) and the highest concentration used in the main experiments, 120.0 µg/mL was determined following a preliminary cytotoxicity range-finding experiment.

In Experiment 1, treatment of cells started approximately 24 hours following mitogen stimulation. In the absence of S-9 this was 20 hours followed by a 28-hour recovery period prior to harvest (20+28). Treatment in the presence of S-9 was for 3 hours followed by a 45-hour recovery period prior to harvest (3+45). The S-9 used was prepared from a rat liver post-mitochondrial fraction (S-9) from Aroclor 1254 induced animals. Concentrations of CD5789 for micronucleus analysis were selected by

evaluating the effect of CD5789 on the replication index. Micronuclei were analyzed at 3 or 4 concentrations, see study conditions below:

Experiment 1 (24 hour PHA)

S-9	Treatment + recovery (h)	Vehicle control	Concentration (µg/mL) CD5789	Percentage Cytotoxicity[a]
-	20+28	0[b]	15.00, 20.00, 25.00, 30.00	65%
+	3+45	0[b]	30.00, 40.00, 60.00	60%

[a] at highest analyzed concentration
[b] vehicle control was DMSO only
PHA = Phytohaemagglutinin

CONCLUSION:

CD5789 did not induce any biologically relevant increases in micronuclei in cultured human peripheral blood lymphocytes following treatment in the absence and presence of a rat liver metabolic activation system (S-9).

72. RDS.03.SRE.12524 - CD5789 Induction of chromosome aberrations in cultured Chinese hamster ovary (CHO) cells in the presence and absence of ultraviolet light.

OBJECTIVE:

The objective of the study was to evaluate the clastogenic potential of CD5789 by its effects on the chromosomes of cultured Chinese hamster ovary (CHO) cells, treated in the absence and presence of ultraviolet light.

MATERIAL AND METHODS:

CD5789 was tested in an *in vitro* cytogenetics assay using duplicate cultures of Chinese Hamster Ovary (CHO) cells in the presence and absence of UV irradiation (including visible light). A preliminary range-finder, covering a broad range of concentrations, was performed in the presence of two doses of UV radiation to investigate the phototoxicity of the chemical, and to determine the concentration range to be used in the main study. The test article was formulated in sterile anhydrous analytical grade DMSO and the highest concentration used in the range-finder was 2500 µg/mL. The doses of UVR used in the preliminary range-finder were 350 and 700 mJ/cm2. All irradiations were performed using an Atlas Suntest CPS+ lamp. This lamp emits radiation across a spectrum similar to that of natural solar radiation, which encompasses UVA and UVB wavelengths.

In the phototoxicity range-finder, there were no marked differences in toxicity following treatment of CD5789 at two UVR doses, indicating no evidence of phototoxicity. Therefore, only one dose of UVA (700 mJ/cm^2) was used in the main experiment. A concentration of 50 µg/mL was chosen as the maximum concentration for the main experiment and a range of concentrations from this used in the absence and presence of UV radiation. Concentrations of CD5789 for chromosome analysis from the irradiated cultures were selected by evaluating the effect of CD5789 on population doublings (PD) relative to concurrent vehicle controls.

Chromosome aberrations were analyzed at 3 different concentrations (see table below).

UV	Treatment + recovery (hours)	Vehicle control	Concentration (µg/mL) CD5789	Percentage Cytotoxicity [b]
-	3+17	0[a]	9.000, 15.00, 18.00	51%
+	3+17	0[a]	9.000, 15.00, 18.00	48%

[a] Vehicle control was DMSO only
[b] At highest analyzed concentration

Appropriate negative (vehicle) control cultures were included in the test system under each treatment condition. The proportion of cells with structural aberrations in these cultures fell within historical vehicle control ranges.

4-Nitroquinoline 1-oxide (NQO) was employed as a positive control in the absence of UV radiation and 8-methoxypsoralen was employed as positive control chemicals in

	the absence and presence of UV light. Both treatments induced increases in the proportion of cells with structural aberrations. When added to cultures treated in the absence of UVR, 8-methoxypsoralen induced frequencies of cells with structural aberrations that were similar to those seen in concurrent vehicle control cultures (non-irradiated). The test system was therefore considered sensitive and valid. CONCLUSION: CD5789 did not induce structural chromosome aberrations in cultured CHO cells in the absence or presence of UV radiation when tested up to its limit of cytotoxicity.
in vivo (including additional toxicokinetic assessment)	**73. RDS.03.SRE.12600 - Induction of micronuclei in the bone marrow of treated rats.** OBJECTIVE: The objective of the study was to assay CD5789 for its genotoxicity in an in vivo micronucleus assay in Sprague Dawley rats. MATERIAL AND METHODS: Groups of 6 male and 6 female rats were treated twice with the vehicle (PEG 400/EtOH/NaCl 0.9% (70/10/20 w/w/w)) or CD5789 (at 3.75, 7.5 or 15 mg/kg/day) via continuous intravenous infusion, in order to maximize exposure of the target organ to the test article. A dose volume of 2.0 mL/kg, at a rate of 0.5 mL/minute, was used for the intravenous infusion administration. Untreated controls were included in the study. A group of 6 male and 6 female rats were treated once with the positive control, Cyclophosphamide (CPA 20 mg/kg), at a dose volume of 5 mL/kg via slow (bolus) intravenous injection on the second day of dosing. Clinical signs observed in the Micronucleus Experiment included lethargy, ataxia and decreased activity. Bone marrow smears were prepared from sacrificed animals approximately 24 hours following the final administration. In addition to the micronucleus animals, groups of male and female satellite animals were dosed with vehicle or CD5789 at 3.75, 7.5 or 15 mg/kg/day. Plasma was isolated from these animals and used to assess systemic exposure to CD5789. CONCLUSION: CD5789 did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of female rats treated up to 15 mg/kg/day (i.v. infusion), the maximum practicable dose in that study. In male rats, no induction of micronuclei was observed at 3.75 and 15 mg/kg/day (i.v. infusion). However a statistically significant increase was noted at 7.5 mg/kg/day, when compared to the vehicle control but there was no statistically significant difference between the MN PCE values in the 1st 2000 PCE in males at 7.5 mg/kg/day and those in the untreated control males. A positive increase at the intermediate group would normally be accompanied by a positive response or evidence of bone marrow toxicity in the high dose group, which was not the case. It was also unusual that the dominant effect has been observed in male rats when exposure to CD5789 was higher in female rats, at all-time points and dose levels. Plasma analysis also confirmed a dose dependent increase in exposure to CD5789 in males and female rats. In addition, the individual MN values in males at the middle dose level were within the range of the background data of the vehicle control. Due to this lack of robustness, this statistical increase in males at 7.5 mg/kg was considered of no toxicological relevance.
4) carcinogenicity:	
long-term studies	**74. RDS.03.SRE.12847 - CD5789 cream 104-week dermal carcinogenicity study in the CD1 mouse.** OBJECTIVE:

The objectives of the study were to evaluate the effects of the test item CD5789 cream on the incidence and morphology of tumors following daily dermal application to the Swiss CD1 mouse for 104 consecutive weeks.

MATERIAL AND METHODS:

The study was conducted according to the following design:

Group/Treatment	Theoretical dose volume (mL/kg/day)	Concentration of formulation (%)	Dose level (mg/kg/day)	Number of animals			
				Main study		Satellite study	
				Males	Females	Males	Females
1. Control (water)	2	0	0	60	60	6	6
2. Placebo I	2	0	0	60	60	6	6
3. Low dose	2	0.001	0.02	60	60	15	15
4. Intermediate dose[a]	2	0.0025	0.05	60	60	15	15
5. High dose[a]	2	0.005	0.1	60	60	15	15
6. Placebo II[a]	2	0	0	60	60	6	6
7. Ultra-low dose[a]	2	0.0005[b]	0.01	60	60	15	15

Note: To comply with FDA recommendations, group 4 and 5 main animals were prematurely sacrificed in week 22 without histopathology examinations and group 4 and 5 satellite animals were discarded without blood sampling.
[a]: After the premature sacrifice of group 4 and 5 main and satellite animals, it was decided to add two new groups (group 6 and 7 animals) in the study on October 24 to 26th 2012, at the request of the Sponsor to comply with FDA recommendations and in agreement with the Study Director.
[b]: According to the results of the formulation analysis of the batch 12.01774 for CD5789 0.0005 % CREAM, the actual concentration of this formulation was 0.00035 % instead of 0.0005 %. At the request of the Sponsor, group 7 animals were treated with this formulation (first day of treatment, 24 October 2012) up to 18 December 2012 (week 8). Group 7 animals were then treated with CD5789 0.0005 % CREAM batch number 12.02481, which concentration was 0.0005 %.

Group 1 animals (control) were handled in exactly the same way as placebo or test item treated animals and they received water for injection by dermal application. Group 2 and 6 animals (placebo) received the placebo (CD 5789 cream placebo) by dermal application. Satellite animals were dedicated to blood sampling for toxicokinetic evaluation after 26 weeks of treatment. They were treated for up to 26 weeks at the same doses as the main study animals. After each blood sampling in week 27, the satellite animals were sacrificed without necropsy.

Treatments were applied on skin areas of approximately 2 x 3 cm corresponding to at least 10% of the total body surface area from the scapular to the lumbar region, clipped free for hair before application and as necessary during the treatment period. Application sites were unprotected and the materials were applied at 2 mL/kg/day. Application sites were washed and dried approximately 6 hours after the application on a weekly basis.

Morbidity/mortality checks were performed at least twice daily. Clinical observations were performed daily. A full clinical examination was performed once every 4 weeks until week 25 then once weekly thereafter. Detailed information concerning visible or palpable masses was recorded. Local tolerance at the application sites was observed once weekly up to week 13 and monthly thereafter. Individual body weights were recorded weekly until week 16, and then once every 4 weeks up to weeks 104/105. Food consumption was measured weekly for each cage of animals for 16 weeks, and then for a one week–period, once every 4 weeks, up to weeks 104/105. Before necropsy of all surviving main group animals and prematurely sacrificed animals, one drop of blood was taken to prepare a blood smear from each animal.

All main group animals which died during the study were necropsied. The surviving animals were sacrificed at the end of the treatment period (between weeks 100 and 105). Tissue samples were fixed and preserved at necropsy for all animals. Selected tissues from groups 1 (water control), 2 (placebo), 3 (low dose), 6 (placebo) and 7 (ultra-low dose) sacrificed at the end of the treatment period, from all animals sacrificed moribund (or sacrificed for ethical reasons) or found dead and all macroscopic abnormalities, masses and nodules were examined histopathologically.

From week 14, severe skin lesions occurred in animals treated with 0.0025% and 0.005% CD5789 cream. To comply with FDA recommendations, all animals treated at 0.0025% and 0.005% CD5789 cream were sacrificed in week 22 without

histopathology, considering that these dose levels were not acceptably tolerated over the course of a 104-week dermal study in mice. In addition, the treatment of two additional groups (new placebo group and ultra-low dose 0.0005% CD5789 group) started under the same experimental conditions described above.

CONCLUSION:

Two-year dermal application of CD5789 cream at 0.0005% and 0.001%, corresponding respectively to doses of 0.01 and 0.02 mg/kg/day, to Swiss CD1 mice did not cause any increase in the incidence of primary or metastatic neoplastic conditions.

There was an increased incidence of sores/crusts and of scaly appearance of treated skin in both treated groups. These changes were more severe in males, leading to increased incidence of moribund animals and premature sacrifice of many animals for ethical reasons. These lesions on treated skin correlated with microscopic findings (in the form of scab/ulceration and epidermal hyperplasia/hyperkeratosis).

At both concentrations, toxicokinetic evaluation after 26 weeks of treatment showed that animals were exposed to CD5789. AUC0-24h at 0.001% (0.02 mg/kg/day) was 8.64 and 10.5 ng.h/mL, in males and females respectively.

The higher tested concentrations of 0.0025% and 0.005% (0.05 and 0.1 mg/kg/day respectively) were not tolerated. They induced severe skin lesions on treated areas from week 14 of treatment, leading to the early sacrifice of these groups.

75. RDS.03.SRE.12846 - CD5789 104-week oral (gavage) carcinogenicity study in the Wistar rat.

OBJECTIVE:

The objectives of the study were to evaluate the effects of the test item CD5789 on the incidence and morphology of tumours following daily oral (gavage) administration to the Wistar rat for 104 consecutive weeks.

MATERIAL AND METHODS:

The study was conducted according to the following design:

Group/Treatment	Dose volume (mL/kg/day)	Dose concentration (mg/mL)		Dose level (mg/kg/day)		Number of animals: Main study		Number of animals: Satellites	
		M	F	M	F	M	F	M	F
1. Control	2	0	0	0	0	60	60	6	6
2. Low dose	2	0.05	0.025	0.1	0.05	60	60	9	9
3. Intermediate dose	2	0.15	0.05	0.3	0.1	60	60	9	9
4. High dose	2	0.375	0.1	0.75	0.2	60	60	9	9

M: males; F: females

Group 1 animals (control) received the vehicle [0.5 % (w/v) carboxymethyl cellulose (300-600 centipoises at 2 %) and 0.1 % (w/v) Tween 80 in water for injection]. Satellite animals were dedicated to blood sampling for toxicokinetic evaluation in week 27. They were treated for up to 26 weeks at the same doses as the main study animals. After the last blood sampling in week 27, the satellite animals were sacrificed without necropsy.

Morbidity/mortality checks were performed at least twice daily. Clinical examinations were performed daily. A full clinical examination was performed once every 4 weeks until week 25 then once weekly thereafter. Detailed information concerning visible or palpable masses were recorded. Individual body weights were recorded weekly until week 16 and once every 4 weeks thereafter up to week 104. Food consumption was measured weekly for each cage of animals for 16 weeks, then for a one week period once every 4 weeks up to week 104.

	All main group animals which died or were sacrificed for ethical reasons or moribund status during the study were necropsied. The surviving animals were sacrificed and necropsied at the end of the treatment period (between weeks 105 to 107). Tissue samples were fixed and preserved for all animals. Histopathology examination was conducted on selected tissues from control and high dose animals sacrificed at the end of the treatment period, from all animals sacrificed moribund (or sacrificed for ethical reasons) or found dead and all macroscopic abnormalities, masses and nodules. Histopathological examination was performed from the group 2 and/or 3 animals (low and intermediate doses) sacrificed at termination, for any macroscopic findings. CONCLUSION: Under the defined experimental conditions of the study, daily administration of CD5789 to the Wistar rat at 0.1, 0.3 or 0.75 mg/kg/day in the males or 0.05, 0.1, 0.2 mg/kg/day in the females for 104 weeks did not cause any effect on the incidence and morphology of tumors. The treatment resulted in a dose-related slightly lower body weight gain from 0.3 mg/kg/day in the males and from 0.1 mg/kg/day in the females. The treatment at the high dose of 0.75 mg/kg/day (males) and 0.2 mg/kg/day (females) induced non-neoplastic changes in the stomach, femur/tibia and skin. Only skin changes were noted in the intermediate dose groups, males and females, and in the low dose male group. The toxicokinetic evaluation after 26 weeks of treatment showed that animals treated with CD5789 were exposed to CD5789. The AUC0-24h was 68.4 and 174 ng.h/mL in high dose males and females respectively.
short-term or middle-term studies	Not Applicable
additional studies	Not Applicable
5) reproductive and developmental toxicity:	
effect on fertility and early embryonic development	**76. RDS.03.SRE.12759 - CD5789 Fertility toxicity study by the oral route (gavage) in the rat (Segment I).** OBJECTIVE: The objectives of the study were to evaluate the effects of CD5789, on gonadal function, mating behavior and reproductive performance in the Wistar rat when administered during gametogenesis, mating and early gestation. MATERIAL AND METHODS: The test item, CD5789, was administered by oral gavage at dose levels of (males/females) 0.1/0.05, 0.5/0.1, and 0.75/0.2 mg/kg/day to 3 groups of 20 male and 20 female Wistar rats. The males were treated for four weeks and the females for two weeks before pairing. Treatment then continued throughout mating and up to necropsy of the males or until Day 7 of gestation inclusive for the females. A fourth group received the vehicle (0.5% Carboxy Methyl Cellulose and 0.1% Tween 80 in water for injection) at the same dose volume (2 mL/kg). Clinical condition and body weights were monitored throughout the study for all animals. Food consumption was measured during the pre-mating period for males and females and during gestation for the females. The males were sacrificed after approximately 8 weeks of treatment (after completion of caesarean examinations) and submitted to a necropsy examination. The testes and epididymides were weighed and an automated sperm analysis was performed. The inseminated females were submitted to a caesarean examination on day 13 of gestation for examination of their uterine contents. At necropsy, the females were examined macroscopically and litter parameters were recorded. The ovaries of the females were also weighed. Selected

	reproductive organs from males and females were fixed and preserved in appropriate fixatives at necropsy. CONCLUSION: After oral (gavage) of the Wistar rat with CD5789 at dose levels of 0.1/0.05, 0.5/0.1 or 0.75/0.2 mg/kg/day (males/females) there was no effect of treatment on mating performance or fertility and no adverse macroscopic or weight changes associated with the reproductive organs. The no observed adverse effect level (NOAEL) for gonadal function, mating behavior and reproductive performance in the male was 0.75 mg/kg/day. The NOAEL for gonadal function, mating behavior, reproductive performance and early gestation in the female was 0.2 mg/kg/day.
embryotoxicity	**77. RDS.03.SRE.12516 - CD5789 Embryo-fetal toxicity, dose range-finding study by the oral route (gavage) in the pregnant rat.** OBJECTIVE: The objectives of the preliminary study were to provide information for the selection of appropriate dose levels for a subsequent embryo-fetal toxicity study in the rat with CD5789. MATERIAL AND METHODS: CD5789 was administered once daily by gavage at dose levels of 0.03, 0.10, 0.30 and 1.00 mg/kg/day to groups of 6 mated female Sprague-Dawley rats from Days 6 to 17 of gestation inclusive. A fifth group of 6 mated rats received the vehicles, 0.5 % CMC (w/v) with 0.01 % (w/w) Tween 80 and served as a control. Maternal clinical condition, body weights and food consumption were monitored throughout the study. Females were submitted to a caesarean examination on Day 20 of gestation. At necropsy, females were weighed, examined macroscopically and kidneys and gravid uterus were weighed. Litter parameters were recorded and all fetuses were weighed, sexed and examined for external abnormalities. Selected maternal organs/tissues were sampled and preserved. A histopathology examination was performed for the stomach and kidneys of all adult females. Blood samples were taken from 6 satellite females per group at specific time-points on Days 6 and 17 of gestation for a toxicokinetic evaluation in plasma. CONCLUSION: After repeated oral administration, the AUC0-24h was 2 to 2.5 fold higher for each dose at the end of dosing period (GD17) than after the first administration (GD6) suggesting some degree of accumulation of CD5789. Although there was no mortality, treatment at 1.00 mg/kg/day was the maximum tolerated dose due to a marked deterioration in clinical condition of the dams during the last week of gestation with clear reductions in maternal body weight gain and food consumption. Treatment-related microscopic changes, principally including acanthosis/hyperkeratosis, were also noted in the non-glandular portion of the stomach at this dose. Embryo-fetal toxicity was also restricted to the high dose group and included a markedly lower mean live litter size due to high post-implantation loss, and lower mean fetal weight, compared with the control group. The teratogenic potential of CD5789 was clearly demonstrated with 100 % of the available fetuses in the high dose group presenting a syndrome of multiple malformations. There were no similar findings in the lower dose groups, so the no observed effect level (NOEL) for both maternal and embryo-fetal toxicity was considered to be 0.30 mg/kg/day. It is recommended that the high dose in a subsequent embryo-fetal development study should not exceed 1.00 mg/kg/day so the severity of the maternal response is not further exacerbated. **78. RDS.03.SRE.12521 - CD5789 Embryo toxicity study by the oral route (gavage) in the rat (Segment II).** OBJECTIVE:

The objectives of the main study were to evaluate the effects of CD5789 on the maternal condition and on embryonic and the fetal development in the rat.

MATERIAL AND METHODS:

CD5789 was administered once daily by gavage at dose levels of 0.03, 0.10, 0.30 and 1 mg/kg/day to groups of 25 mated female Sprague-Dawley rats from Days 6 to 17 of gestation inclusive. A fifth group of 25 mated females received a similar volume (5 mL/kg) of the vehicle 0.5 % (w/v) CMC with 0.01 % Tween 80 (w/w) in water for injection and served as a control. Satellite groups of 6 mated female Sprague-Dawley rats received the same dosing regimen. In addition, on Days 6 and 17 of gestation, the CD5789 was combined with radiolabeled [14C]-CD5789 radioactive doses of 0.06, 0.20, 0.60 and 2.00 µCi/kg/administration. Blood samples were taken from the satellite animals at specific time-points on Days 6 and 17 of gestation and plasma was prepared for bioanalysis of unlabeled CD5789 using HPLC with ESI-MS-MS detection and [14C]-CD5789 using Accelerator Mass Spectrometry. Maternal clinical condition, body weights and food consumption were monitored throughout the study. Females were submitted to a caesarean examination on Day 20 of gestation. At necropsy, animals were examined macroscopically, the gravid uterus was weighed and all fetuses were weighed, sexed and examined for external abnormalities. Half of the fetuses were examined internally prior to processing for skeletal examination. The remaining fetuses were preserved for fixed-visceral examination by the modified Wilson-Barrow technique.

CONCLUSION:

For both CD5789 and [14C]-CD5789, toxicokinetic evaluations demonstrated that the systemic exposure was proportional to the dose demonstrating toxicokinetic linearity. Systemic exposure was proportional to dose levels at Day 6 and at Day 17 of gestation, demonstrating that repeat administration of CD5789 did not affect the toxicokinetics. There was no carry-over of CD5789 from Day 6 to Day 17; elimination was complete over the study duration for both Day 6 and Day 17 of gestation. No systemic accumulation was observed across the dose range at either Day 6 or Day 17 of gestation.

Treatment at doses of 0.30 and 1 mg/kg/day from Days 6 to 17 of gestation was associated with clear maternal effects (principally dose-related reductions in mean maternal body weight gain and food consumption). The maternal NOEL was 0.10 mg/kg/day.

Treatment at 1 mg/kg/day was associated with a high incidence of embryo-fetal death and reduced fetal weight compared with the control group. The teratogenic potential of CD5789 was also demonstrated at 0.30 and 1 mg/kg/day with a syndrome of multiple external, visceral and/or skeletal abnormalities. There were also treatment-related increases in the incidences of less severe skeletal anomalies and variations in the 0.10 mg/kg/day compared with the control group.

The only overt treatment-related findings in the 0.03 mg/kg/day group were increased incidences of unilateral or bilateral rudimentary 14th ribs and incomplete ossification of the 6th sternebra compared with the control group. These minor changes, which are present in the historical control data, were considered to be of no major physiological consequence.

The NOAEL for embryo-fetal toxicity was therefore considered to be 0.03 mg/kg/day (AUC0-24h of 52.54 and 56.76 ng.h/mL on Days 6 and 17 of gestation respectively). Plasma analyses were performed without enzymatic hydrolysis.

79. RDS.03.SRE.12517 - CD5789 Embryo-fetal toxicity, dose range-finding study by the oral route (gavage) in the pregnant rabbit.

OBJECTIVE:

The objective of this preliminary study was to provide information for the selection of appropriate dose levels for a subsequent embryo-fetal toxicity study in the rabbit.

MATERIAL AND METHODS:

CD5789 was administered once daily by gavage at dose levels of 0.01, 0.05, 0.25 and 1.00 mg/kg/day to groups of 6 mated female NZW rabbits from Days 6 to 19 of gestation inclusive. A fifth group of 6 mated rabbits received the vehicle, 0.5 % (w/v) carboxymethylcellulose (CMC with 0.01% (w/w) Tween 80 and served as a control. Maternal clinical condition, body weights and food consumption were monitored throughout the study. Females were submitted to a caesarean examination on Day 29 of gestation. At necropsy, females were examined macroscopically and kidneys and gravid uterus were weighed. Litter parameters were recorded and fetuses were weighed and examined for external abnormalities. Selected maternal organs/tissues were sampled and preserved. A histopathology examination was performed for the stomach and kidneys from all adult females. Blood samples were taken from all animals at specific time-points on Days 6 and 19 of gestation for a toxicokinetic evaluation in plasma.

CONCLUSION:

Drug exposure was demonstrated only at the 2 highest doses (0.25 and 1 mg/kg/day). The systemic exposure of CD5789 was low and increased proportionally with dose after one single or repeated oral administration. There was no evidence of accumulation of CD5789 after repeated administration. There was no obvious evidence of maternal or embryo-fetal toxicity in any group at doses up to 1.00 mg/kg/day inclusive. It is therefore recommended that higher doses should be investigated to try and elicit a maternal response to treatment with CD5789.

80. RDS.03.SRE.12520 - CD5789 Embryo toxicity study by the oral route (gavage) in the rabbit (Segment II).

OBJECTIVE:

The objective of this main study was to evaluate the effect of CD5789 on the embryonic and fetal development of the New Zealand White rabbit.

MATERIAL AND METHODS:

CD5789 was scheduled to be administered by the oral route (gavage) once daily by gavage at dose levels of 0.5, 5 and 50 mg/kg/day (groups 2, 3 and 4 respectively) to groups of 22 mated female New Zealand White rabbits from Days 6 to 19 of gestation inclusive. Due to a marked treatment-related maternal response, administration was terminated on Day 14 or 15 for the high dose group. A fourth group of 22 mated rabbits received a similar volume (5 mL/kg/day) of the control vehicle (0.5 % (w/v) carboxymethylcellulose with 0.5 % (w/w) Tween 80 in water for injection) and served as a control (group 1). Satellite groups of 4 mated female New Zealand White rabbits received the same dosing regimen. In addition, on Day 6 and 19 of gestation (Day 14 for the high dose group), CD5789 was combined with radiolabeled test item ([14C]-CD5789) at radioactive doses of 0.5, 5 and 50 µCi/kg/administration. Blood samples for toxicokinetics were taken from main study and satellite females at specific time-points on Days 6 and 19 of gestation (or 14 for the high dose group) and plasma was prepared for bioanalysis of CD5789 using HPLC with LC-MS/MS detection, and bioanalysis of [14C]-CD5789 using Accelerator Mass Spectrometry. Clinical condition, body weights and food consumption were monitored throughout the study. Surviving females were submitted to a caesarean examination on Day 29 of gestation for examination of their uterine contents, including examination of the placentae, and litter parameters were recorded. At necropsy, females were examined macroscopically and live fetuses were weighed. Fetuses were then examined for external and visceral internal abnormalities and sexed. Heads of approximately half of the fetuses were fixed

	for internal examination by serial sectioning. The eviscerated carcasses of all fetuses were processed for skeletal examination. CONCLUSION: For both, CD5789 (with or without hydrolysis) and [14C]-CD5789, toxicokinetics demonstrated that the systemic exposure was proportional to the dose, demonstrating toxicokinetic linearity. Systemic exposure was proportional to the respective dose levels at Day 6 and at Day 19 (or Day 14 for 14C levels at 50 mg/kg) of gestation, demonstrating that repeat administration of CD5789 did not affect toxicokinetics. There was no carry-over of CD5789 from Day 6 to Day 19 (or Day 14 for 14C levels at 50 mg/kg) and elimination was complete over the study duration for both Day 6 and Day 19 of gestation. No systemic accumulation was observed across the dose range up to Day 19. Enzymatic hydrolysis demonstrated that CD5789 is highly conjugated and that conjugated metabolite was the major plasma circulating drug-related substance. Treatment of the pregnant rabbit with CD5789 at 50 mg/kg/day was above the maximum tolerated dose with mortality, marked effects on the clinical condition, body weight change and food consumption of the females. There were no maternal effects of treatment in the lower dose groups. The NOEL for maternal toxicity was therefore at 5 mg/kg/day. Treatment at 50 mg/kg/day was associated with a high incidence of early embryonic death; only one female had a small litter (n=2) of viable fetuses at term. Both of the fetuses had multiple treatment-related defects. In addition, the teratogenic potential of CD5789 was also clearly demonstrated at the dose of 5 mg/kg/day with 15 % of the fetuses presenting one or more malformations, mainly skeletal changes in the lower vertebral column comparable with changes in the high dose group. Consistent with these observations, less severe findings principally included anomalies (skeletal and/or external) of the tail in over 40 % of the fetuses. The only overt treatment-related finding in the 0.5 mg/kg/day group was a slightly higher incidence of fetuses with a bent tail (usually resulting from a malpositioned caudal vertebra) compared with concurrent control and historical control data. In isolation, this minor change was considered to be of no major physiological significance. Therefore, the NOAEL for embryo-fetal toxicity was set at 0.5 mg/kg/day. The corresponding plasma AUC0-24h was 6.36 and 10.44 ng.h/mL on Days 6 and 19 of gestation, respectively, if the analysis was performed without enzymatic hydrolysis and 337.26 and 829.68 ng.h/mL on Days 6 and 19 of gestation, respectively if the analysis of plasma samples was performed with enzymatic hydrolysis.
prenatal and postnatal toxicity	**81. RDS.03.SRE.12758 - CD5789 Pre- and postnatal development study by the oral route (gavage) in the Wistar rat (Segment III).** OBJECTIVE: The objectives of the study were to evaluate the effects of the test item CD5789 on the embryo-fetal and peri- and postnatal development of the Wistar rat and subsequent reproductive performance of the offspring. MATERIAL AND METHODS: Three groups of 25 mated female Wistar rats were given 2 mL/kg/day of the test item CD5789 by daily oral gavage at dose levels of 0.01, 0.03 and 0.1 mg/kg/day from Day 6 of gestation (i.e. GD6) until postnatal day 20 (i.e. PND 20). A control group of 25 rats was given 2 mL/kg/day of the vehicle [0.5 % (w/v) carboxymethylcellulose (300-600 centipoises at 2 %) and 0.1 % (w/w) Tween 80 in water for injection]. F0 satellite animals were added for toxicokinetic measurements. Clinical condition, body weight and food consumption of the females were monitored during gestation and lactation. The females were allowed to give birth. The pre-weaning viability, growth and development of the F1 offspring were evaluated. F1 litter sizes (including satellite animals) were standardized by culling on PND 4. Litter parameters, including the

	number of pups born, pup survival and pup weights were recorded up to PND 21. At least one male and one female pup were selected from each litter to form the F1 generation. The dams and unselected pups were necropsied on PND 21. F0 females and unselected F1 offspring were submitted to a macroscopic examination. Groups of 3 or 6 satellite F0 dams were sampled on GD6 (first day of treatment) and on PND 20 (last day of treatment) at 1, 2, 4, 8 and 24 hours post dose in order to determine the test item concentration in maternal plasma. Designated unselected satellite pups from all groups were sampled on PND 4 and PND 20 in order to determine test item concentration in fetal plasma. Analyses were performed using a validated LC-MS/MS method. The selected F1 offspring were maintained untreated for monitoring of post-weaning development, behavioral tests and mating to form a second generation. Body weights of the F1 females were monitored during the pre-mating and mating periods and during gestation. Body weights of the F1 males were monitored from selection up to necropsy. The study was terminated with the necropsy of the F1 males after the caesarean examinations of the F1 females on day 13 *post-coitum*. All F1 animals were submitted to a macroscopic examination. The pregnancy status, number of corpora lutea and numbers and types of uterine implantations were determined for the females. CONCLUSION: There was no adverse effect of maternal treatment on pre- or postnatal development or reproductive performance of the offspring in any group. The No Observed Adverse Effect Level (NOAEL) for the F0 females and for the embryo-fetal and peri- and postnatal development of the rat and subsequent reproductive performance of the offspring was therefore 0.1 mg/kg/day (AUC0-24h of 90.1 ng.h/mL on day 6 of gestation and 63.0 ng.h/mL on postnatal day 20).
studies in which the medicinal product is administered to offspring (non-mature animals) and/or evaluated for long-term effects	**82. RDS.03.SRE.12984 - CD5789 4-week oral (gavage) dose range-finding study in the juvenile beagle dog.** OBJECTIVE: The objectives of this dose-range finding toxicity study were to assess the tolerability of CD5789 and to generate exposure data following daily oral administration to the juvenile beagle dog for 4 consecutive weeks (between postnatal days 21/22 and 49/50). MATERIAL AND METHODS: Four litters were included in the study, each being allocated to a single group. The study was conducted according to the following design:

Group/Treatment	Dose level (mg/kg/day)	Dose volume (mL/kg/day)	Dose concentration (mg/mL)	Number of puppies	
				Males	Females
1. Control	0	2	0	2	4
2. Low dose	0.01	2	0.005	3	3
3. Intermediate dose	0.04	2	0.02	3	3
4. High dose	0.16	2	0.08	3	3

Group 1 puppies (control) received the vehicle (0.5 % (w/v) carboxymethyl cellulose and 0.1 % (w/v) Tween 80 in water for injection).

The following parameters were assessed: morbidity/mortality, clinical observations including behaviour assessment, growth measurements (tibia length and standing shoulder height), sexual maturation (vaginal opening, testicular migration to the scrotum), ophthalmology, body weight, haematology, coagulation, serum clinical chemistry analysis, levels of CD5789 in plasma (using a validated LC MS/MS method with a limit of quantification: 0.05 ng/mL).

	All surviving animals were euthanized after week 4 and examined for macroscopic findings. Selected organs were weighed. Histopathology evaluation was performed on selected tissues and organs. CONCLUSION: Daily oral administration to the juvenile beagle dog (from postnatal day 21/22) for 4 consecutive weeks of CD5789 at dose levels up to 0.16 mg/kg/day was well tolerated and did not induce any adverse effects. The No Observed Adverse Effect level (NOAEL) was established at 0.16 mg/kg/day, corresponding in week 4 to a Cmax of 51.1 ng/mL in males and 64.3 ng/mL for females, and an AUC0-6h of 211 ng.h/mL for males and 255 ng.h/mL for females.
6) local tolerability	**Acute dermal irritation** **83. RDS.03.SRE.12613 - Acute Dermal Irritation in Rabbits.** OBJECTIVE: The aim of this study was to assess the skin irritation potential of CD5789 100 µg/g gel in the New Zealand White rabbit. MATERIAL AND METHODS: A single dose of 0.5 mL of the undiluted placebo or CD5789 100 µg/g gel was placed on a dry gauze pad which was applied to scarified and non-scarified clipped skin areas of 3 male rabbits. CD5789 100 µg/g gel or placebo was applied on the skin for 24 hours using an occlusive hypoallergenic dressing. Cutaneous reactions were observed 24, 48 and 72 hours after application of CD5789 100 µg/g gel or its placebo, and then on Days 5, 6, 7 and 8. The mean scores of erythema and edema recorded for all animals after 24 and 72 hours were calculated to obtain the Cutaneous Primary Irritation Index (CPII). CONCLUSION: When applied topically to rabbits, the CD5789 100 µg/g gel was irritant. **84. RDS.03.SRE.12735 - CD5789 0.005% Cream Primary Skin Irritation Study in Rabbits (24-Hour Semi-Occlusive Application).** OBJECTIVE: The aim of this study was to assess the primary skin irritation potential of CD5789 50 µg/g cream A in the rabbit. MATERIAL AND METHODS: The test item and the placebo cream were applied by topical semi-occlusive application of 0.5 mL to the intact left flank (test item) or the right flank (placebo) of three young adult New Zealand White rabbits. The duration of treatment was twenty-four hours. The scoring of skin reactions was performed 1, 24, 48 and 72 hours, as well as 7 and 10 days after removal of the dressing. CONCLUSION: Based upon the CPII of 1.25 calculated according to the procedure requested by the Applicant, CD5789 50 µg/g cream A is considered to be "slightly irritating" to rabbit skin. **Repeated Dermal irritation** 13 weeks (see Section 2) multiple-dose toxicity) and in minipigs for up to 9 months (see Section 2) multiple-dose toxicity). CD5789 in other formulations was tested for up to 13 weeks in dermal studies in mice, rats and minipigs (see section 7) additional toxicity studies/ other). Consequently, no specific repeat dermal irritation studies were performed as CD5789 was found to induce dose-related skin irritation in all species,

consistent with the pharmacological class of the compound, with the minipig being the most sensitive one.

Screening studies were performed during CD5789 formulation development in minipigs applying tests compounds and reference retinoids on small skin areas (approximately 2.8 cm2) for 4 weeks, called 'mini-zone' studies. These studies do not bring any additional safety information on CD5789 formulated in the cream. Consequently, they are only listed below. Six studies were performed: **RDS.03.SRE.8614**, **RDS.03.SRE.8625**, **RDS.03.SRE.8636**, **RDS.03.SRE.8679**, **RDS.03.SRE.8691** and **RDS.03.SRE.8718**.

85. **RDS.03.SRE.8614 - 4-week exploratory study in the Göttingen minipig: evaluation of the dermal tolerance of selected retinoids when applied on minizones followed by a 3-week recovery period.**
86. **RDS.03.SRE.8625 - CD0271/CD1579 AND CD5789 4-week dermal tolerance study screening between different formulation concepts in the Göttingen® minipig followed by a 2-week recovery period.**
87. **RDS.03.SRE.8636 - CD5789 4-week dermal tolerance study screening between different formulations in the Göttingen® minipig.**
88. **RDS.03.SRE.8679 - CD5789 4-week dermal tolerance study screening between different formulations in the Göttingen minipig.**
89. **RDS.03.SRE.8691 - CD5789 4-week dermal tolerance (minizones) study screening between different formulations in the Göttingen minipig.**
90. **RDS.03.SRE.8718 - CD5789 screening of different formulations in the Göttingen® minipig. 3-week preliminary phase followed by a 4-week dermal tolerance study (minizones).**

Ocular irritation

91. **RDS.03.SRE.12994 - A primary eye irritation study of CD5789 Cream in rabbits.**

OBJECTIVE:

The aim of this study was to assess the ocular irritation potential of CD5789 Cream 25 µg/g, 50 µg/g and placebo in female Japanese White rabbits.

MATERIAL AND METHODS:

CD5789 25 µg/g, 50 µg/g cream and cream placebo were applied at 0.1 mL/eye in the left eyes of 3 female Japanese White rabbits /group. The right eye served as a control for each animal. For each treatment, one group had no eye washing after application and another group had an eye washing with a 30 seconds contact period with 100 mL of water for injection, at 30 seconds after the application. In the washed eye group, the right eye was washed with the same procedure as the treated left eye. Ocular reactions were observed approximately 1 hour, 24, 48 and 72 hours after the administration.

CONCLUSION:

CD5789 cream at up to 50µg/g was non irritating when administered by the ocular route to rabbits.

92. RDS.03.SRE.12614 - Acute eye irritation in rabbits.

OBJECTIVE:

The aim of this study was to assess the ocular irritation potential of CD5789 100 µg/g gel in the New Zealand White rabbit.

MATERIAL AND METHODS:

In the first administrated male New Zealand White rabbit CD5789 100 µg/g gel was found non severely irritant; CD5789 100 µg/g gel was then evaluated simultaneously in 2 other animals. Ocular reactions were observed approximately 1 hour, 24, 48 and

72 hours after the administration and then on Days 5 and 8. The recorded irritation reactions were used to calculate a maximum ocular irritation index.

CONCLUSION:

CD5789 100 µg/g gel was irritating when administered by the ocular route to rabbits.

93. RDS.03.SRE.12987 - A primary eye irritation study of CD5789 Cream HE1 in rabbits.

OBJECTIVE:

The aim of this study was to assess the ocular irritation potential of CD5789 Cream HE1 Japanese White rabbits.

MATERIAL AND METHODS:

CD5789 100 µg/g, 200 µg/g and 400 µg/g cream HE1 and cream HE1placebo were applied at 0.1 mL/eye in the eyes of 3 animals/group. The right eye served as a control for each animal. For each treatment, one group had no eye washing after application and another group had an eye washing after a 30-second contact period with 100 mL of water for injection. In the washed eye group, the right eye was washed with the same procedure as the treated left eye. Ocular reactions were observed approximately 1 hour, 24, 48 and 72 hours after the administration.

CONCLUSION:

CD5789 cream HE1 at up to 400 µg/g was minimally irritating when administered by the ocular route to rabbits.

Skin sensitization

94. RDS.03.SRE.12995 - A skin sensitization study of CD5789 Cream in guinea pigs (Buehler Test).

OBJECTIVE:

The objective of this study was to assess the skin sensitization potential of CD5789 cream in the Buehler Test.

MATERIAL AND METHODS:

The study consisted of four groups of female Hartley strain white guinea pigs: a test article sensitization group (10 animals), a base sensitization group (10 animals), a positive control group (5 animals) and a negative control group (5 animals). Induction was done 9 times with CD5789 cream 50 µg/g or with the base (0 µg/g) for the base sensitization group, by dermal applications every 2 or 3 days for a total duration of 19 days. Then, the animals were subjected to challenge with the test article at low concentration (25 µg/g) or the base (0 µg/g), after a 2-week rest period. For the positive control group, animals were subjected to induction for sensitization 9 times with 1-Chloro-2,4-dinitrobenzene (DNCB) at 1% concentration and then subjected to challenge with DNCB at 0.25% concentration or with the vehicle (ethanol). For the negative control group, the animals were subjected to induction of sensitization only with the patch, and then subjected to challenge with the test article at low concentration (25 µg/g), base (0 µg/g), 0.25% DNCB solution or ethanol. The skin reactions were observed at 24 and 48 hours after removal of challenge application to evaluate the skin sensitization.

CONCLUSION:

Neither CD5789 50 µg/g Cream, nor its base showed skin sensitization induction under the conditions of this study.

95. RDS.03.SRE.8601 - CD5789 assessment of contact hypersensitivity in the mice local lymph node assay.

OBJECTIVE:

The objective of this study was to assess the skin sensitization potential of CD5789 gel in the Local Lymph Node Assay (LLNA).

MATERIAL AND METHODS:

CD5789 gel was used at 300 µg/g (undiluted) or diluted 2-fold and 4-fold in the placebo gel. Control groups were treated either with hexyl cinnamic aldehyde 25% in vehicle [acetone/olive oil (4:1, v/v)] considered as the positive control, or with the vehicle [acetone/olive oil (4:1, v/v)] alone considered as the negative control.

During 3 consecutive days, 25 µL of the vehicle, drug product placebo, drug product, drug product dilutions in placebo or positive control solution were applied topically on the dorsum of both ears of each mouse. After a rest period of 2 days, animals received intravenously (via the tail vein) 20 µCi of 3[H]-methyl thymidine in 250 µL of PBS. Five (5) hours after injection, animals were sacrificed and the auricular draining lymph nodes removed and pooled on an individual animal basis. A cell suspension was prepared and the 3[H]-methyl thymidine incorporation into the DNA of divided lymphocytes was measured by □-scintillation counting as disintegration per minute over a period of 10 minutes. Results were compared with those of the negative control group which was treated with the vehicle [(acetone/olive oil, 4:1 v/v)] alone.

CONCLUSION:

CD5789 gel placebo has no sensitization potential. CD5789 gel at 75, 150 and 300 µg/g, is a skin sensitizing agent, as the SI values were above 3 for the three concentrations tested.

96. RDS.03.SRE.12983 - A skin sensitization study of CD5789 Cream HE1 in guinea pigs (Buehler Test).

OBJECTIVE:

The objective of this study was to assess the skin sensitization potential of CD5789 cream HE1 in the Buehler Test.

MATERIAL AND METHODS:

The study consisted of four groups of female Hartley strain white guinea pigs: a test article sensitization group (10 animals), a base sensitization group (10 animals), a positive control group (5 animals) and a negative control group (5 animals). Induction was done 9 times with CD5789 cream HE1 400 µg/g and 9 times with the base (0 µg/g) for the base sensitization group, by dermal applications every 2 or 3 days for a total duration of 19 days. Then, the animals were subjected to challenge to the test article at low concentration (100 µg/g) or the base (0 µg/g), after a 2-week rest period. For the positive control group, animals were subjected to induction for sensitization 9 times with 1-Chloro-2,4-dinitrobenzene (DNCB) at 1% concentration and then subjected to challenge at 0.25% concentration or to the vehicle (ethanol). For the negative control group, the animals were subjected to induction of sensitization only with the patch, and then subjected to challenge to the test article at low concentration (100 µg/g), base (0 µg/g), 0.25% DNCB solution or ethanol. The skin reactions were observed at 24 and 48 hours after removal of challenge application to evaluate the skin sensitization.

CONCLUSION:

Neither CD5789 Cream HE1 nor its base showed skin sensitization induction under the conditions of this study.

Photoirritation and photosensitization

97. RDS.03.SRE.12615 - Photoirritation and photosensitization by cutaneous route in guinea pigs.

OBJECTIVE:

	The aim of this study was to assess the photoirritation and photosensitization potential of CD5789 100 µg/g gel in the guinea pig. MATERIAL AND METHODS: Twenty-five (25) Hartley Crl guinea pigs were allocated to 3 treatment groups. The study design was as follows: **Group / Number of animals / Induction phase (4 applications - Days 1 to 4) / Challenge application (Day 22)** **Anterior left flank / Anterior right flank / Posterior left flank / Posterior right flank / Scoring** 1 / 10 / CD5789 100 µg/g gel / None / CD5789 100 µg/g gel / None / 1, 4, 24 48 h 2 / 10 / CD5789 100 µg/g gel + UV / Placebo + UV / CD5789 100 µg/g gel + UV / Placebo + UV 3 / 5 / Placebo +UV / UV / CD5789 100 µg/g gel + UV / UV The photoirritation potential of CD5789 was evaluated after the first treatment and/or irradiation performed on Day 1 in animals of all 3 groups. The photoirritation potential of CD5789 was evaluated on Day 22 following a challenge phase by topical application with or without UVA + UVB irradiation to the posterior area of the right and left flanks of the animals. For each treatment, a dose-volume of 0.1 mL of CD5789 100 µg/g gel or placebo was applied by cutaneous route. The irradiation doses of UVA and UVB were infra-erythematogenic. Cutaneous reactions were evaluated at the treatment sites. CONCLUSION: Topical applications of CD5789 100 µg/g gel or of its placebo followed by UV irradiation did not induce any photoirritant reactions in the guinea pig. A photosensitizing potential of the test item was observed with a higher incidence than with the placebo (80% animals versus 40%, respectively). However due to the irritation observed in the induction period, no clear conclusion can be drawn from the results.
7) additional toxicity studies:	Not Applicable
antigenicity (formation of antibodies)	Not Applicable
immunotoxicity	Not Applicable
study of mechanisms of action	Not Applicable
drug addiction	Not Applicable
toxicity of metabolites	Not Applicable
toxicity of impurities	Not Applicable
other	**Studies by dermal route with other CD5789 formulations** **98. RDS.03.SRE.8695 - CD5789 4-week local tolerance (dermal application) study in the CD1 mice.** OBJECTIVE: The objective of the study was to assess the local tolerance of CD5789 formulated in gel (Klucel gel) and cream A formulations in CD1 mice.

MATERIAL AND METHODS:

CD5789 formulated in a gel (Klucel gel) and cream A at 100µg/g was applied at 2 mL/kg/day corresponding to a daily dose of 0.2 mg/kg to 8 CD1 mice /sex/group for 4 weeks. Water for injection (absolute control), Gel and Cream A placebos were applied under the same conditions and served as negative controls. At the end of the dosing period, necropsy examinations were performed, and selected tissues were microscopically examined.

CONCLUSION:

CD5789 when dermally applied in Gel or Cream A at 0.01% was not well tolerated in CD1 mice. The skin was identified as the only target organ in both sexes, all changes being related to the pharmacological activity of the test item.

99. RDS.03.SRE.8789 - CD5789 4-week local tolerance (dermal application) study in the CD-1 mice.

OBJECTIVE:

The objectives of this study were to assess the local tolerance of CD5789 formulated in HE1 cream to CD1 mice upon repeated daily dermal application for 4 consecutive weeks and to compare it with a CD5789 cream group. Results are focused on the CD5789 cream group.

MATERIAL AND METHODS:

CD5789 cream HE1 at 50, 100 and 200 µg/g and cream at 100 µg/g were applied at 2 mL/kg/day for 4 weeks to 6 CD1 mice/sex/group, corresponding to CD5789 dose levels of 0.1, 0.2 and 0.4 mg/kg/day with the HE1 formulation and 0.2 mg/kg/day with the cream formulation. Animals were treated without protection for 6 hours after which the application sites were rinsed with lukewarm water.

CONCLUSION:

CD5789 cream applied at 0.2 mg/kg/day induced erythema with edema, males being more affected than females.

100. RDS.03.SRE.8813 - CD5789 Cream 13-week dermal application toxicity study in the CD1 mice.

OBJECTIVE:

The objectives of the present study were to assess the local tolerance and systemic toxicity of CD5789 formulated in HE1 cream to CD1 mice for 13 consecutive weeks and to compare it with a CD5789 cream group.

MATERIAL AND METHODS:

Male and female CD1 mice (12/group/sex, approximately 9 weeks old) were topically treated with CD5789 cream HE1 at dose-levels of 0.02, 0.1, 0.2 mg/kg/day under an application-volume of 2 mL/kg/day. CD5789 cream at 0.2 mg/kg/day was used as comparator. A control group was treated with CD5789 cream HE1 placebo under the same conditions. The dosage form was applied on approximately 10% of total body surface area. Application sites were not protected and were rinsed once a week. The design of the study is summarized in Table 20.

Table 20 Design of the 13 week dermal application toxicity study in the CD1 Mice

Group/treatment	Drug Substance concentration in formulation (%(w/w))	Formulation dose-volume (mL/kg/day)	Drug substance dose (mg/kg/day)	Amount of formulation applied (mg/cm²)*	Number of animals per sex
1/ Cream HE1 Placebo	0	2	0	12	12 (P) 6 (S)
2/ CD5789 0.001% Cream HE1	0.001	2	0.02	12	12 (P) 12 (S)
3/ CD5789 0.005% Cream HE1	0.005	2	0.1	12	12 (P) 12 (S)
4/ CD5789 0.01% Cream HE1	0.01	2	0.2	12	12 (P) 12 (S)
5/ CD5789 0.01% Cream	0.01	2	0.2	12	12 (P) 12 (S)

P: principal animals for main groups; S: satellite animals for TK evaluation
*estimation based on 10% of body surface = approximately 5 cm^2 calculated for animals bodyweight of 0.03 kg

Observations and measurements included daily mortality checks, clinical observations, cutaneous reactions and weekly food consumption as well as weekly bodyweight recording. Hematology and serum chemistry investigations were performed at the end of the dosing period. During the last week of dosing, blood and skin samples (skin biopsies at application sites) were taken from satellite animals for determination of CD5789 concentrations. Concentrations were determined by LC-MS/MS method (LOQ = 0.1 ng/mL, validated method for plasma and LOQ = 0.125 ng/mL, non-validated method for skin). At the end of the dosing period, necropsy examinations were performed for all principal animals with organ weight recordings. All required organs/tissues were microscopically examined in high dose principal animals, control group and comparator group, and as per study plan criteria, a limited list of organs/tissues were examined for mid and low dose animals.

CONCLUSION:

At 0.2 mg/kg/day, CD5789 cream HE1 induced slightly less marked cutaneous reaction than CD5789 cream, which is correlated to the CD5789 delivered concentrations in total skin: CD5789 cream delivers 4 to 6.5 times more CD5789 than cream HE1 in total skin of males and females respectively. Macroscopic, microscopic and clinical pathology parameters effects identified between these two groups were roughly similar.

101. RDS.03.SRE.8598 - CD5789 3-week dermal dose range finding toxicity study in the Wistar rat.

OBJECTIVE:

The objective of this dose range finding study was to determine the highest dose of gel formulations to be used in a subsequent 4-week dermal toxicity study.

MATERIAL AND METHODS:

Groups of 2 male and 2 female Wistar rats were treated once daily by topical application for 3 consecutive weeks. During the dosing period, application sites were protected by a non-occlusive jacket in order to avoid oral ingestion of the test item formulations. CD5789 concentrations of 10, 100 and 300 µg/g were tested at dose-volumes of 1 ml/kg/day or 2 ml/kg/day. This design permitted the assessment of 6 different dose levels (from 0.01 to 0.6 mg/kg/day). Placebo was applied at the dose-volume of 2 mL/kg/day under the same experimental conditions. Mortality was checked at least twice daily. Animals were monitored for clinical signs daily, a detailed physical examination was performed, animals were weighed and food consumption calculated weekly. Evaluation of cutaneous reactions on treatment-site was performed daily approximately 6 hours after treatment.

CONCLUSION:

The maximal tolerated dose was determined for CD5789 gel at 100 µg/g, using a dosing volume of 1 mL/kg (corresponding to 0.1 mg/kg/day drug substance applied).

102. RDS.03.SRE.8595 - CD5789 4-week topical (dermal application) toxicity study in the Wistar rat.

OBJECTIVE:

The aim of this study was to assess the local and systemic toxicity of CD5789 gel in the Wistar rat for 4 weeks.

MATERIAL AND METHODS:

Treatment groups consisted of 10 males and 10 females each. Animals treated with CD5789 gel received topical doses of 0.01, 0.02 and 0.1 mg/kg, controls animals received the placebo gel. Animals were regularly monitored for clinical signs, body weight and food consumption. At the end of the 4-week treatment period, hematology, coagulation and serum chemistry parameters were analyzed, urinalysis was performed, and all animals were sacrificed and underwent necropsy. Selected organs were weighed and subjected to histopathological evaluation. Skin (treated and not treated), stomach, kidneys and bone (sternum and femur) were also examined in the intermediate dose groups.

In addition, satellite animals (6 per sex in treated groups and 3 per sex in control) were used to assess the plasma drug level and toxicokinetic parameters on Day 1 and 21 (LLOQ: 0.25 ng/mL).

CONCLUSION:

All doses of CD5789 gel induced dose-related cutaneous signs of irritation and/or edema in all treated-animals. No adverse systemic effects were observed at up to 0.1 mg/kg/day, equivalent to CD5789 100 µg/g gel and applied to approximately 10% of the total surface area at 1mL/kg. The systemic exposure to the parent compound at this highest dose level (AUC0-24h at Day 21) was 19.28 ng.h/mL and 59.91 ng.h/mL in males and females, respectively.

103. RDS.03.SRE.8667 - CD5789 gel 4-week topical (dermal application) administration toxicity study in the Göttingen minipig.

OBJECTIVE:

The objectives of the study were to assess the local tolerance and systemic toxicity of CD5789 gel to Göttingen® minipigs and to assess toxicokinetic parameters.

MATERIAL AND METHODS:

Groups of 4 male and 4 female Göttingen minipigs were topically treated for at least 4 consecutive weeks with CD5789 gel at 0.001%, 0.005% or 0.01% (corresponding to 10, 50 or 100 g/g) at the dosing volume of 2 mL/kg. The corresponding doses were 0.02 mg/kg, 0.1 mg/kg/day and 0.2 mg/kg/day respectively. Control group was treated with CD5789 gel placebo, using the same procedure of administration. The dosage form was spread over two application-sites to achieve a total percentage of body surface treated of approximately 10%. Treated areas were protected during 6 hours (or 24 hours during weekends and public holidays). After the exposure period (non-occlusive) local tolerance at the application-sites was evaluated and application-sites rinsed. Morbidity/mortality checks were performed at least twice daily. Clinical observations were performed at least once daily. Food consumption was estimated daily and individual body weight was recorded once a week. Cardiovascular and ophthalmological examinations were performed during pre-dosing and week 4. Clinical pathology investigations were performed during pre-dosing and week 4. All animals were sampled for toxicokinetic evaluation on the first day of treatment and after 14 and 28 days of treatment. At the end of the dosing period (between Day 29 and

Day 31), necropsy examinations were performed, organ weights were recorded and selected tissues were microscopically examined.

CONCLUSION:

No systemic toxicity occurred. Topical application of CD5789 gel at 0.001% was tolerated for 4 weeks. At the concentration of 0.005% and 0.01%, adverse cutaneous reactions occurred on treatment-sites, namely erythemas associated in some occasions with edema, leading to interrupt treatment for ethical reasons. Associated microscopic findings consisted of acanthosis, hyperkeratosis with multifocal parakeratosis, presence of crusts, dermal inflammatory infiltrates sometimes associated with edema. In the most severe cases, the presence of ulcers was observed at both dose-levels.

104. RDS.03.SRE.8672 - CD5789 Cream A 4-week topical (dermal application) administration toxicity study in the Göttingen minipig.

OBJECTIVE:

The objectives of the study were to assess the local tolerance and systemic toxicity of CD5789 cream A to Göttingen minipigs and to assess toxicokinetic parameters.

MATERIAL AND METHODS:

Groups of 4 male and 4 female Göttingen minipigs were topically treated for 4 consecutive weeks with CD5789 cream A at 0.001% or 0.005% (corresponding to concentrations of 10 and 50 µg/g) at the dosing volume of 2 mL/kg. The corresponding doses were 0.02 mg/kg/day and 0.1 mg/kg/day respectively. Control group was treated with CD5789 cream A placebo, using the same procedure of administration. The dosage form was spread over two application-sites to achieve a total percentage of body surface treated of approximately 10%. Treated areas were protected during 6 hours exposure period (or 24 hours during weekends and public holidays). After the exposure period (non-occlusive) local tolerance at the application-sites was evaluated and application-sites rinsed. Morbidity/mortality checks were performed at least twice daily. Clinical observations were performed at least once daily. Food consumption was estimated daily and individual body weight was recorded once a week. Cardiovascular and ophthalmological examinations and clinical pathology investigations were performed during pre-dosing and Week 4. All animals were sampled for toxicokinetic evaluation on the first day of treatment and after 28 days of treatment. The limit of quantification of the bioanalytical method was 0.05 ng/mL. At the end of the dosing period, after at least 29 days of treatment, necropsy examinations were performed, organ weights were recorded and selected tissues were microscopically examined.

CONCLUSION:

The daily dermal application of CD5789 cream A at 0.001% and 0.005% did not induce any systemic effects. At the sites of application, the treatment at both concentrations induced dose-related cutaneous effects mainly consisting of erythema and/or edema, which led to interrupt treatment in several animals. After a few days wash out period, there was generally a good recovery that allowed resumption of treatment. Associated microscopic findings were consistent with local irritation and mainly consisted of acanthosis, hyperkeratosis, inflammatory infiltrates in dermis and parakeratosis, with a dose-effect relationship. Local irritation was also noted for one animal treated with the placebo.

105. RDS.03.SRE.8734 - 4-week dermal application toxicity study in the Göttingen minipigs - LC - MS/MS Determination of CD5789 in plasma samples.

OBJECTIVE:

The objectives of the study were to assess the local tolerance, systemic toxicity and plasma concentrations of CD5789 formulated in cream HE1 to Göttingen minipigs.

MATERIAL AND METHODS:

Groups of 3 Göttingen® minipigs/sex were treated dermally for 4 consecutive weeks with CD5789 formulated in the HE1 cream at 0 (placebo), 0.01%, 0.02% and 0.04%, applied at 0.25 mL/kg/day, corresponding to 0.025, 0.05 or 0.1 mg of CD5789/kg/day. The formulation was applied on two different application-sites to achieve a total percentage of treated body surface of approximately 10%. Treated areas were protected (non-occlusive) during 6 hours (or 24 hours during non-working days) then application sites were rinsed with lukewarm water. Cutaneous reactions at the application sites were evaluated 24 hours after each dosing. Morbidity and mortality were checked at least twice daily. Bodyweights were recorded weekly and food consumption was estimated daily. Clinical pathology investigations (hematology, coagulation and serum chemistry) were performed during pre-dosing and during week 5. All animals were sampled for toxicokinetic evaluation after 29 days of treatment on blood samples taken 0.5, 1, 2, 4, 8 and 24h after the last application. A validated LC-MS/MS method was used for the determination of CD5789 in plasma samples (LOQ = 0.05 ng/mL). At the end of the dosing period, necropsy examinations were performed, organ weights were recorded and selected tissues were microscopically examined, including retinoid-specific target organs.

CONCLUSION:

CD5789 when applied in the HE1 cream formulation was detected in plasma samples of 12 out of 18 animals with more exposure at the highest concentration. Plasma concentrations remained in the range of 0.0505 to 0.329 ng/mL. The only dose-related observation associated with the treatment was a dermal irritation associated mainly with acanthosis, hyperkeratosis, spongiosis with or without images of exocytosis and dermal inflammatory infiltrates.

106. RDS.03.SRE.12801 - CD5789 Cream A 13-week topical (dermal application) toxicity study in the Göttingen minipig.

OBJECTIVE:

The objectives of the study were to assess the local tolerance and systemic toxicity of CD5789 cream A to Göttingen minipigs and to determine the systemic exposure.

MATERIAL AND METHODS:

CD5789 formulated in cream A at 10 µg/g, 25 µg/g or 50 µg/g was applied at 1 mL/kg/day to minipigs corresponding to dose levels of 0.01, 0.025 or 0.05 mg/kg/day. Formulations were applied on clipped areas (back and sides of the trunk) representing 10 % of the whole body area and held in contact with the skin with a non-occlusive dressing for 6 hours. The treated area was then rinsed with lukewarm water. The following criteria were assessed: morbidity/mortality, clinical observations, local tolerance, ophthalmology, body weight, food consumption, cardiovascular examinations, hematology, coagulation, serum clinical chemistry, urinalysis, levels of CD5789 in plasma (validated LC-MS/MS method, Limit of Quantification: 0.05 ng/mL). All animals were necropsied at the end of the treatment period and examined for macroscopic lesions. Selected organs were weighed. Histopathological evaluation was performed on selected tissues and organs.

CONCLUSION:

There were no systemic effects after topical application of CD5789 cream A at a dose up to 50 µg/g (0.005%) and a volume of 1mL/kg/day for 13 weeks, in relation to the very low CD5789 systemic exposure measured. The only noteworthy effects consisted of a dose-related, slight to moderate erythema at the application sites.

107. RDS.03.SRE.102318 - CD5789 cream HE1 - 13-week topical (dermal application) toxicity study in the Göttingen minipig.

OBJECTIVE:

The objectives of the study were to determine the local tolerance and systemic toxicity of CD5789 cream HE1 to Göttingen minipigs and to determine the concentrations of CD5789 in plasma samples.

MATERIAL AND METHODS:

CD5789 formulated in HE1 cream at 0.005 %, 0.01 % and 0.02 % was administered daily at 0.25 mL/kg/day (corresponding to 12.5 µg/kg/day, 25 µg/kg/day and 50 µg/kg/day of CD5789, respectively) by dermal application to 4 Göttingen minipigs/sex/group for 13 consecutive weeks. Animals were topically exposed to the test item for approximately 6 hours per day on approximately 10 % of the whole body surface. Group 1 animals (control) received the placebo (CD5789 cream placebo). The following parameters were assessed: morbidity/mortality, clinical observations, local tolerance, ophthalmology, body weight, food consumption, cardiovascular examinations, hematology, coagulation, serum clinical chemistry, urinalysis and levels of CD5789 in plasma at the end of the treatment period (using a validated bioanalytical LC-MS/ MS method, with a limit of quantification of 0.05 ng/mL). All animals were necropsied and examined for macroscopic lesions at the end of the treatment period. Selected organs were weighed. Full histopathological evaluation was performed in all animals.

CONCLUSION:

After daily topical applications of CD5789 cream HE1 at 0.005 %, 0.01 % and 0.02 %, all CD5789 plasma concentrations were below the limit of quantification. The treatment was well tolerated and did not result in any systemic effect. Only minor local reactions occurred at the application sites in all groups, mainly consisting of very slight and/or well-defined erythema with associated minimal histological findings, which did not show any clear dose-relationship and corresponded to the expected local reactions following topical application of a retinoic acid receptor-agonist.

Study by oral route with CD5789

108. RDS.03.SRE.8665 - CD5789 4-week oral (gavage) administration toxicity study in the CD1 mice.

OBJECTIVE:

The objectives of the study were to determine the systemic toxicity of CD5789 to CD1 Mice upon repeated oral administration and to determine the concentrations of CD5789 in plasma samples.

MATERIAL AND METHODS:

Mice received daily oral doses of 0.1, 0.5, 1 or 5 mg/kg/day CD5789, whereas control animals were treated with the vehicle alone (CMC 0.5%/ Tween 80 at 0.1% in water), for at least 4 consecutive weeks.

The observations were the following: morbidity/mortality, clinical signs, body weights and food consumptions. All animals were submitted to necropsy. Selected organs were weighed and a limited list of organs and tissues were fixed for microscopic examination.

Blood samples from additional satellite animals were taken on day 25 for proof of exposure.

CONCLUSION:

Male and female CD1 Mice orally treated with doses of 0.1, 0.5, 1 and 5 mg/kg/day CD5789 for four consecutive weeks were exposed to test-item. Histopathological examination identified the skin, stomach and bones, as target organs.

5. Conclusions on non-clinical studies

The Applicant concludes that the nonclinical data generated adequately demonstrate the pharmacological activity, pharmacokinetics and safe profile of CD5789 and CD5789 50 µg/g cream in the proposed clinical conditions of use for the topical treatment of acne vulgaris. As for other retinoids, CD5789 induced hypervitaminosis-A syndrome, after sufficient systemic exposure. By the oral route, teratogenicity in the rabbit represented the most sensitive endpoint for nonclinical safety evaluation of CD5789, with a safety margin of 98 in terms of systemic exposure, when compared to the most exposed subject under maximal clinical use conditions in human (study RD.06.SRE.18337). CD5789 is not genotoxic nor carcinogenic. Following chronic dermal application of CD5789 cream in minipigs, there were very low or non detectable systemic exposure and no systemic effects, but only expected and reversible local dermal reactions. CD5789 50 µg/g cream was not irritating after single eye administration in rabbits and showed no skin sensitization potential in guinea pigs.

In conclusion, the safety testing conducted with CD5789 cream and its active drug substance supports the intended clinical use.

Applicant (Marketing Authorization Holder)	(signature) Régis Schulz (full name)	**GALDERMA SA** Zählerweg 10 CH-6300 Zug 058 455 85 00

Annex 30
to the Procedure for expertise of registration materials for medicinal products submitted for state registration (renewal), as well as expertise of the materials on variations to the registration materials during the marketing authorization validity period
(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-03-SPR-40128 - Plasma and skin pharmacokinetic and skin pharmacodynamic study of CD 5789 in different doses and different formulations following repeated topical applications over 4 weeks in adult healthy subjects
6. Clinical study phase	Phase 1 human pharmacology study
7. Clinical study period	Date of first screened: 04 April 2011 Date of last subject completed: 20 June 2011
8. Countries where clinical study was conducted	France - Belgium
9. Number of subjects	Approximately 70 healthy volunteers were to be screened in order to enroll 60 subjects (10 per group).
10. Aim and	Primary objectives:

secondary purposes of clinical study	- To assess the systemic exposure of CD 5789 after repeated once daily topical application over 4 weeks of different concentrations and formulations, throughout pharmacokinetic parameters in healthy subjects treated on at least a 1000 cm^2 body surface area. Secondary objectives - To evaluate CD 5789 skin distribution at different concentrations and formulations (25 µg/g, 50 µg/g, 100 µg/g ; gel, cream A, cream B); - To investigate pharmacodynamic activity of CD 5789 in skin biopsies (retinoid-like activities / inflammation); - To investigate systemic CD 5789 metabolites (if any).
11. Clinical study design	Multi-centre, randomized study open study in 6 parallel groups: - Group A: CD 5789 25 µg/g gel formulation - 1000 cm^2; - Group B: CD 5789 50 µg/g gel formulation - 1000 cm^2; - Group C: CD 5789 50 µg/g gel formulation - 2000 cm^2; - Group D: CD 5789 100 µg/g gel formulation - 1000 cm^2; - Group E: CD 5789 50 µg/g cream A formulation - 1000 cm^2; - Group F: CD 5789 50 µg/g cream B formulation – 1000 cm^2.
12. Main inclusion criteria	Key inclusion criteria: - Adult male or female healthy subjects aged 18 to 65 years old; - Body weight between 45 and 100 kg at the Screening visit; - Body Mass Index (BMI) between 18 and 30 kg/m^2 at the Screening visit; - If male, the subject had agree to shave the facial treatment area the evening prior to any of the designated clinic visits, and had to agree to only use their routine shaving regimen for any shaving regimen for the duration of the study; - If female of childbearing potential, they had to agree to use a highly effective double-barrier contraception method for the duration of the study and three months after the last product application.
13. Investigational medicinal product, method of administration, strength	CD5789, topical administration (gel), strength : 25 µg/g ; 50 µg/g and 100 µg/g CD5789, topical administration (Cream A), strength : 50 µg/g CD5789, topical administration (Cream B, strength : 50 µg/g
14. Reference medicinal product, method of administration, strength	None
15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	Not Applicable
17. Safety evaluation	Adverse events were to be reported throughout the study. Adverse events with an onset date on or after the date of the administration of the first treatment were classified as

criteria	treatment emergent.
	- Systemic safety
	  ○ Vital signs (blood pressure, pulse rate)
	  ○ Physical examination at Baseline and end of treatment
	  ○ Routine laboratory parameters (hematology, blood chemistry)
	- Cutaneous safety
	  ○ Local tolerability assessments (erythema, scaling, dryness, and stinging/burning sensation separately on the face on a 4-point scale (0 = None to 3 = Severe)). The same tolerability assessments were also to be performed separately for the other treated areas (back and chest).

18. Statistical methods	The following variables were summarized by descriptive statistics: - Demographics and baseline characteristics; - Physical examination, vital signs (blood pressure and pulse rate); - Routine laboratory parameters (hematology, blood chemistry, urinalysis); - Cutaneous safety (local tolerability assessments); - Adverse events (AEs). - Systemic pharmacokinetics If quantifiable, plasma concentration parameters were to be submitted, after logarithmic transformation (Ln), to an analysis of variance, in order to evaluate separately, time and group factors. Skin PK parameters were to be submitted after logarithmic transformation (Ln), to an analysis of variance. The model included group as factor and 90% confidence intervals of the pairwise differences between groups on the Ln scale were to be calculated. Limits of the intervals were to be back-transformed into exponential to obtain 90% confidence intervals of the ratios of geometric means between groups, on the original scale. The following contrasts were to be performed for the analysis of the group factor: Formulation effect: - CD 5789 50 µg/g gel – 1000 cm^2 *versus* CD 5789 50 µg/g cream A – 1000 cm^2 - CD 5789 50 µg/g gel – 1000 cm^2 *versus* CD 5789 50 µg/g cream B – 1000 cm^2 - CD 5789 50 µg/g cream A – 1000 cm^2 *versus* CD 5789 50 µg/g cream B – 1000 cm^2 Dose proportionality: - CD 5789 100 µg/g gel - 1000 cm^2 *versus* CD 5789 50 µg/g gel - 1000 cm^2 - CD 5789 100 µg/g gel - 1000 cm^2 *versus* CD 5789 25 µg/g gel - 1000 cm^2 - CD 5789 50 µg/g gel - 1000 cm^2 *versus* CD 5789 25 µg/g gel - 1000 cm^2 For the PK/PD relationship, fold (Day 6/ Baseline) of expression of specific genes were to be plotted against Skin PK parameters and Pearson correlation coefficients were to be calculated overall.
19. Demographic indicators of the study population (gender, age, race, etc.)	From the 117 subjects screened, 60 subjects were included in the pharmacokinetic and safety analyses, 10 per arm, from 2 centers were randomized into 6 treatment groups. One subject in group cream B 50 µg/g / 1000 cm^2 experienced at Day 22 a severe skin irritation on the treated area, considered related and leading to permanent discontinuation. The mean age was 44 years, ranging from 20 to 64 years. Thirty two (32; 53.3%) of the subjects were females. All except one subject (Black) were Caucasians. Mean body mass indices (BMI) across groups ranged between 23.4 and 25.4 kg/m^2. Detailed information about demographic is provided in Table 1.

Table 1 Demographic

		Cream A 50 µg/g / 1000 cm²	Cream B 50 µg/g / 1000 cm²	Gel 25 µg/g / 1000 cm²	Gel 50 µg/g / 1000 cm²	Gel 50 µg/g / 2000 cm²	Gel 100 µg/g / 1000 cm²	TOTAL
Age in Years	N	10	10	10	10	10	10	60
	Mean	42.50	47.50	42.40	42.10	41.80	48.00	44.05
	SD	15.83	14.16	13.99	12.50	17.70	12.77	14.22
	Median	40.50	48.00	40.00	41.50	41.00	50.50	42.50
	Min~Max	21~62	25~64	22~64	25~61	20~64	29~62	20~64
	Q1~Q3	26~58	40~61	33~54	35~56	24~58	35~60	33~58
Gender	N	10	10	10	10	10	10	60
	Female	6 (60.0%)	3 (30.0%)	5 (50.0%)	5 (50.0%)	7 (70.0%)	6 (60.0%)	32 (53.3%)
	Male	4 (40.0%)	7 (70.0%)	5 (50.0%)	5 (50.0%)	3 (30.0%)	4 (40.0%)	28 (46.7%)
Race	N	10	10	10	10	10	10	60
	Black	-	1 (10.0%)	-	-	-	-	1 (1.7%)
	Caucasian	10 (100.0%)	9 (90.0%)	10 (100.0%)	10 (100.0%)	10 (100.0%)	10 (100.0%)	59 (98.3%)
Body Mass Index (kg/m²)	N	10	10	10	10	10	10	60
	Mean	23.62	24.19	23.40	25.41	23.91	24.49	24.17
	SD	2.55	2.95	2.04	2.93	1.88	2.84	2.54
	Median	22.81	23.99	23.52	26.15	24.17	25.53	24.04
	Min~Max	20~28	19~28	21~26	20~29	20~26	19~28	19~29
	Q1~Q3	22~26	23~27	21~25	23~28	23~25	24~26	23~26
Height (cm)	N	10	10	10	10	10	10	60
	Mean	166.3	175.2	171.3	173.4	170.6	168.0	170.8
	SD	9.10	10.74	10.27	10.52	7.46	8.09	9.54
	Median	168.0	179.5	173.0	175.0	173.0	167.0	171.5
	Min~Max	150~177	157~188	152~187	157~187	157~182	157~186	150~188
	Q1~Q3	161~174	166~184	164~178	162~183	164~175	163~172	164~177
Weight (kg)	N	10	10	10	10	10	10	60
	Mean	65.40	74.87	69.13	76.62	69.63	69.53	70.86
	SD	9.39	15.28	11.74	12.56	7.74	12.37	11.88
	Median	63.75	72.90	73.50	76.30	68.80	69.60	70.50
	Min~Max	52~82	55~100	54~85	57~97	60~79	51~91	51~100
	Q1~Q3	59~71	63~88	57~78	68~88	61~77	62~78	61~80

20. Efficacy outcomes	Not Applicable
21. Safety outcomes	Safety was assessed by considering adverse events and evaluating local tolerability as well as standard laboratory testing and vital signs assessments. **- Adverse events** No SAEs were reported. Overall 38 healthy subjects (63.3%) experienced 96 adverse events. Thirty-one subjects (31; 51.6%) experienced 55 adverse event(s) related to the study drug. All the related AE but 2 were classified in "Skin and subcutaneous tissue disorder" system organ class; they were principally pruritus and skin irritation. The 2 other related AEs were coded as hot flush. On Day 22, one subject in group cream B 50µg/g 1000 cm² experienced on the treated area severe skin irritation considered related and leading to permanent discontinuation. Headache, nausea and nasopharyngitis were the main unrelated AEs.

Table 4 **Overview of adverse events**

	Cream A 50 µg/g / 1000 cm² (N=10)		Cream B 50 µg/g / 1000 cm² (N=10)		Gel 25 µg/g / 1000 cm² (N=10)		Gel 50 µg/g / 1000 cm² (N=10)		Gel 50 µg/g / 2000 cm² (N=10)		Gel 100 µg/g / 1000 cm² (N=10)	
	N events	N(%) subjects	N events	N(%) subjects	N events	N(%) subjects	N events	N(%) subjects	N events	N(%) subjects	N events	N(%) subjects
All AEs	21	7 (70.0%)	10	6 (60.0%)	6	3 (30.0%)	15	8 (80.0%)	24	8 (80.0%)	20	6 (60.0%)
Related AEs	14	7 (70.0%)	8	6 (60.0%)	4	3 (30.0%)	8	5 (50.0%)	12	6 (60.0%)	9	4 (40.0%)
All dermatologic AEs	13	7 (70.0%)	8	6 (60.0%)	4	3 (30.0%)	8	5 (50.0%)	14	6 (60.0%)	9	4 (40.0%)
Related dermatologic AEs	13	7 (70.0%)	8	6 (60.0%)	4	3 (30.0%)	8	5 (50.0%)	12	6 (60.0%)	8	4 (40.0%)
All serious AEs	0	0	0	0	0	0	0	0	0	0	0	0
Related serious AEs	0	0	0	0	0	0	0	0	0	0	0	0
Severe AEs	0	0	1	1 (10.0%)	0	0	1	1 (10.0%)	0	0	1	1 (10.0%)
Related severe AEs	0	0	1	1 (10.0%)	0	0	1	1 (10.0%)	0	0	1	1 (10.0%)
AEs of Special Interest	0	0	1	1 (10.0%)	0	0	0	0	0	0	0	0
Related AEs of Special Interest	0	0	1	1 (10.0%)	0	0	0	0	0	0	0	0
AEs leading to discontinuation	0	0	1	1 (10.0%)	0	0	0	0	0	0	0	0
Related AEs leading to discontinuation	0	0	1	1 (10.0%)	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0	0	0	0	0

Adverse events are defined as events occurred after the first use of medication

Numbers in columns cannot be added because a given subject may have reported more than one AE.

Pruritus was the most often reported symptom (24 subjects) with the application of CD5789. This was confirmed for CD5789 50 µg/g cream A (6 subjects) and CD5789 50 µg/g gel at 2000 cm² (5 subjects). Skin irritation considered related to the study drug was reported in 15 subjects; the most often after application of the gel at 50 µg/g and cream A. Details are provided in Table 5.

Table 5 **Summary of related adverse events by SOC and by preferred term (Safety population)**

		Cream A 50 µg/g 1000 cm² (n=10)	Cream B 50 µg/g 1000 cm² (n=10)	Gel 25 µg/g 1000 cm² (n=10)	Gel 50 µg/g 1000 cm² (n=10)	Gel 50 µg/g 2000 cm² (n=10)	Gel 100 µg/g 1000 cm² (n=10)
TOTAL NUMBER OF AEs		14	8	4	8	12	9
TOTAL NUMBER OF SUBJECTS WITH AEs		7 (70.0%)	6 (60.0%)	3 (30.0%)	5 (50.0%)	6 (60.0%)	4 (40.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		7 (70.0%)	6 (60.0%)	3 (30.0%)	5 (50.0%)	6 (60.0%)	4 (40.0%)
	Pruritus	6 (60.0%)	4 (40.0%)	3 (30.0%)	3 (30.0%)	5 (50.0%)	3 (30.0%)
	Skin irritation	3 (30.0%)	2 (20.0%)	-	4 (40.0%)	4 (40.0%)	2 (20.0%)
	Pruritus generalised	1 (10.0%)	-	-	-	1 (10.0%)	2 (20.0%)
	Skin hypopigmentation	1 (10.0%)	-	-	-	-	-
	Skin hyperpigmentation	-	1 (10.0%)	-	-	-	-
	Purpura	-	-	-	-	-	1 (10.0%)
VASCULAR DISORDERS		1 (10.0%)	-	-	-	-	1 (10.0%)
	Hot flush	1 (10.0%)	-	-	-	-	1 (10.0%)

	- Local tolerability Local tolerability (Erythema, Scaling, Dryness and Stinging/Burning) was assessed on a 4-point scale before the morning study application; separately for each treated area (face, back and chest) from baseline to the end of study. Change of treated area was permitted in case of skin irritation. Except for erythema (worst mean score of 2.20 with CD5789 100 µg/g / 1000 cm²) worst mean scores of signs and symptoms during treatment with topical CD5789 formulations did not exceed 2.0 (moderate). None of the mean scores for cream A and cream B at 50 µg/g exceeded 1.6 at any application site. No sign and symptom was scored severe during treatment with CD5789 50 µg/g cream B. **- Laboratory testing, Vital signs assessments** There were no changes in standard laboratory parameters and vital signs between screening and end of treatment visit, no changes in physical findings were reported.
22. Summary (conclusion)	Repeated topical application of CD5789 formulations during 4 weeks in 60 healthy male and female subjects and under maximized conditions (2 mg/cm²) resulted in: - Unquantifiable plasma exposure with the gel at 25 µg/g, cream A formulation at 50 µg/g and cream B formulation at 50 µg/g (up to 1000cm² treated). - Very low systemic exposure with the gel at 50 µg/g (up to 2000 cm² treated) and 100 µg/g (up to 1000 cm² treated). The most exposed subject had a C_{max} of 30 pg/mL and an AUC0-24 of 297 pg.h/mL after 29 day of topical application of gel at 50 µg/g on 1000 cm². Following the last application, CD5789 was rapidly cleared and was unquantifiable in all subjects 12 hours after the last application. Skin penetration investigation showed a similar skin penetration profile between gel and cream B. A lower level of penetration was obtained with cream A (3-fold higher exposure to CD5789 in skin with the gel in comparison to the cream A). No clear pharmacodynamic effect could be demonstrated. Application of CD5789 50 µg/g cream B resulted in severe skin irritation in one subject, on treated and untreated areas, leading to the withdrawal of the subject. No other subject stopped treatment during the study. There were no serious adverse events and no death reported. Severe local signs and symptoms of skin irritation were reported with CD5789 gel at 50 and 100 µg/g but did not lead to the withdrawal of subjects. There were no changes in standard laboratory parameters and vital signs between screening and end of treatment visit, no changes in physical findings were reported.

Applicant (Marketing Authorization Holder)	(signature) Régis Schulz (full name) GALDERMA SA Zählerweg 10 CH-6300 Zug 058 455 85 00

Annex 30
to the Procedure for expertise of registration materials for medicinal products submitted for state registration (renewal), as well as expertise of the materials on variations to the registration materials during the marketing authorization validity period
(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-03-SPR-40181E - Exploratory study to evaluate the safety and efficacy of CD5789 in subjects with ichthyosis
6. Clinical study phase	Phase 1
7. Clinical study period	Study initiation date: 24 February 2012 Date of last subject: 03 September 2012
8. Countries where clinical study was conducted	France – Germany – United States of America
9. Number of subjects	A total of 33 patients were screened and 31 were randomized at 8 centers in 3 countries (3 in France, 3 in Germany and 2 in the USA) to receive CD5789 100 µg/g Cream B (N=17) or CD5789 50 µg/g Cream B (N=14). All patients received Vehicle Cream B on the contralateral target zone (n=31). Of these 33 patients, 31 patients comprised the

	Safety population and the intent-to-treat (ITT) population and 26 patients were included in the per protocol (PP) population.
10. Aim and secondary purposes of clinical study	- Primary objective: To evaluate the local tolerability and systemic safety of CD5789 100 µg/g and 50 µg/g Simulgel (Cream B) compared to its vehicle, after 6 weeks of once daily, 5 days a week applications on 2 zones in patients with lamellar ichthyosis (LI) or recessive X linked ichthyosis (RXLI). - Secondary objective: To conduct an exploratory assessment of the efficacy of CD5789 100 µg/g and 50 µg/g Cream B compared to the Vehicle.
11. Clinical study design	This was an exploratory, multicenter, randomized, controlled, double-blind, intra-individual (left versus [vs.] right comparison) study in patients with LI or RXLI. The study consisted of an up to 4-week screening period, followed by a 6-week treatment period, during which the study treatments were applied on 2 target zones, once daily, 5 days per week (every day except on weekends). The 2 target zones were treated according to a randomization scheme generated by the Sponsor: ○ 1 zone treated with Active Treatment (CD5789 100 µg/g Cream B or CD5789 50 µg/g Cream B), ○ 1 zone treated with Vehicle Cream B (negative control). The study included 6 visits to the study center: the Screening Visit (Day -27 to Day 0), the Baseline Visit (Day 1), 3 Interim Visits (Day 8±2, Day 15±2, and Day 29±2) and the Final Visit (Day 43±2). The target zones were selected at the Screening Visit and confirmed (or modified) at the Baseline Visit. Patients were randomized to either CD5789 100 µg/g Cream B or CD5789 50 µg/g Cream B on Day 1. Application of study treatments were done by a nurse (first applications) and thereafter by the patient at home (under the supervision of a nurse/personal care assistant during the first week). Four versions of the study protocol were generated to include country-specific requests. The study protocols for each country were identical, with the exception of: i) the ECG being performed at Screening and Final Visit in the centers based in the USA and ii) some inclusion and exclusion criteria.
12. Main inclusion criteria	Key inclusion criterion: Male and female[a] patients, aged 18-65 years, clinically diagnosed with LI or RXLI, presenting with 2 contralateral target zones that had to be 40 cm^2 (6 square inches) in size, located on the dorsal part of the limbs and of identical severity (individual clinical scores ≥2[b] and Baseline total sum score [TSS] identical or differing by 1 grade). [a]For the first 3 patients enrolled at the Hôpital Saint Louis (France), only females of non-childbearing potential were eligible. [b]The Sponsor decided after study initiation not to exclude patients with an erythema score inferior to 2
13. Investigational medicinal product, method of administration, strength	CD5789, cream, topical (non-occlusive) administration, strength: 50µg/g (0.1%) and 100 µg/g (0.005%)
14. Reference medicinal	Vehicle product, cream, topical (non-occlusive), strength: Not Applicable

product, method of administration, strength	
15. Concomitant therapy	Not Applicable
16. Efficacy evaluation criteria	**Efficacy measurements:** Throughout the study, efficacy was assessed by a dermatologist using appropriate scales for disease severity and individual clinical scores. **Primary efficacy criterion:** The primary efficacy criterion was the change in Investigator Global Assessment (IGA) from the Baseline Visit (Day 1) to the Final Visit (Day 43). **Secondary efficacy criteria:** - IGA at each Interim Visit and change from Baseline. - Scaling, roughness and erythema scores at each visit and change from Baseline. - TSS (sum of scaling, roughness and erythema) at each visit and percent change from Baseline. - Investigator's and patient's comparative evaluations of the 2 target zones at Day 43. - Success rate, which was defined as the percentage of patients meeting the following 3 conditions at Final Visit: Scaling =0 or 1, change in scaling from Baseline ≥ 2 and roughness =0 or 1.
17. Safety evaluation criteria	- Local tolerance (irritation and stinging/burning) assessed on each zone at each visit from Day 1 by the Investigator using a 4-point scale (from 0: none to 3: severe). - Laboratory parameters (hematology, biochemistry) at Screening and Final Visit. - Physical examination and vital signs (including an electrocardiogram [ECG], USA only) at Screening and Final Visit. - Adverse Events (AEs) at every visit.
18. Statistical methods	The primary efficacy analysis was based on the PP population, i.e. all patients randomized (excluding patients with major protocol deviations) at each visit. Confirmatory analysis was performed on the ITT population at Baseline and Endpoint Visit only. The Endpoint Visit in the ITT population corresponded to the last observation carried forward (LOCF) used to impute missing post-baseline values. The IGA was analyzed at Final Visit using a Wilcoxon signed rank test for paired data. A non-parametric 90% confidence interval was calculated for the difference between CD5789 Cream B (100 or 50 µg/g) and Vehicle Cream B regarding the absolute change in IGA between Baseline and Final Visit. *Secondary efficacy analysis* The IGA was analyzed at each Interim Visit using a Wilcoxon signed rank test for paired data. The TSS, individual clinical scores and comparative evaluations by the Investigator and the patient were analyzed using a Wilcoxon signed rank test. The success rate was calculated for each study treatment (CD5789 100 µg/g Cream B, CD5789 50 µg/g Cream B and Vehicle). Due to the low sample size, the primary and secondary efficacy analyses consisted in comparing Active Treatment, i.e. CD5789 Cream B (combining the 2 concentrations,

100 and 50 µg/g) with Vehicle Cream B. The statistical tests used to compare Active Treatment and Vehicle Cream B were also conducted separately for each CD5789 concentration.

Post hoc efficacy analysis

Each type of ichthyosis (LI/RXLI) was analyzed separately. There was a change to the planned statistical analysis: a partial sum score (PSS) was calculated as the sum of scaling and roughness scores. The statistical analysis performed on PSS was similar to the one performed on TSS.

19. Demographic indicators of the study population (gender, age, race, etc.)

Table 1 Demographic data – All patients

		Randomized		All
		CD5789 100 µg/g vs. Vehicle	CD5789 50 µg/g vs. Vehicle	
Gender	N	17	14	31
	Male	13 (76.5%)	11 (78.6%)	24 (77.4%)
	Female	4 (23.5%)	3 (21.4%)	7 (22.6%)
Race	N	17	14	31
	White	16 (94.1%)	13 (92.9%)	29 (93.5%)
	Black or African American		1 (7.1%)	1 (3.2%)
	Asian	1 (5.9%)		1 (3.2%)
Age (years)	N	17	14	31
	Mean±SD	37.4±13.3	37.4±13.0	37.4±13.0
	Median	37.0	37.5	37.0
	(Min,Max)	(18,59)	(21,57)	(18,59)

At Baseline, the distribution of gender, race and age in the ITT population was comparable with each CD5789 concentration. The majority of patients were male (24/31, 77.4%), and almost all were Caucasian (29/31, 93.5%). The overall mean (±SD) age was 37.4 (±13.0) years. A total of 21/31 patients (67.7%) had LI and 10/31 patients (32.3%) had RXLI. The distribution of each type of ichthyosis was similar with each CD5789 concentration.

20. Efficacy outcomes

Primary efficacy criterion

Table 3 Absolute change in IGA from Baseline – PP population

Change from D01		CD5789 100 µg/g vs. Vehicle				
		Active	Vehicle	A - V	90%CI[a]	P-value[b]
Day 43 /PP	N	13	13	13	[-2.50;-0.49]	0.066
	Mean±SD	-1.8±2.0	-0.5±1.6	-1.2±2.4		
	Median	-2.0	0.0	-2.0		
	(Min,Max)	(-5,2)	(-3,2)	(-5,5)		
Change from D01		CD5789 50 µg/g vs. Vehicle				
		Active	Vehicle	A - V	90%CI[a]	P-value[b]
Day 43 /PP	N	13	13	13	[-2.01;0.01]	0.230
	Mean±SD	-1.7±2.3	-0.8±1.7	-0.9±2.4		
	Median	-2.0	0.0	-1.0		
	(Min,Max)	(-6,2)	(-4,2)	(-4,4)		
Change from D01		CD5789 in overall vs. Vehicle				
		Active	Vehicle	A - V	90%CI[a]	P-value[b]
Day 43 /PP	N	26	26	26	[-2.00;-0.50]	0.036
	Mean±SD	-1.7±2.1	-0.7±1.6	-1.1±2.3		
	Median	-2.0	0.0	-1.5		
	(Min,Max)	(-6,2)	(-4,2)	(-5,5)		

A: Active Treatment, V: Vehicle.

[a] non parametric 90% confidence interval

[b] p-value regarding the comparison between Active Treatment and Vehicle (Wilcoxon rank signed test).

Between Baseline and Day 43, there was a greater decrease in IGA with Active Treatment

(-1.7±2.1 points) than with Vehicle (-0.7±1.6 points). The difference between Active Treatment and Vehicle was 1.1±2.3 points on a scale of 10, which was statistically significant (p=0.036).

Similar results were found in the ITT population (p<0.01).

The decrease in IGA between Baseline and Day 43 was also greater with Active Treatment than Vehicle for each CD5789 concentration. The difference between Active Treatment and Vehicle was 1.2±2.4 points (100 µg/g) and 0.9±2.4 point (50 µg/g), without reaching statistical significance.

Secondary efficacy criteria

Between Baseline and Day 43, there was a greater decrease in TSS with Active Treatment (-31.0±33.2%) than with Vehicle (-11.0±27.4%). The difference between Active Treatment and Vehicle was -20.1±40.7%, which was statistically significant (p=0.028). Over the same period, scaling and roughness scores decreased by 1.1±1.2 and 1.2±1.0 points with Active Treatment, respectively, whereas they remained stable with Vehicle (-0.1±0.7 and -0.2±0.7 point, respectively). In contrast, the erythema score remained stable with Active Treatment (+0.2±1.3 point), whereas it decreased slightly (-0.5±0.8 point) with Vehicle. These differences between study treatments were all statistically significant (p<0.05).

There was a greater decrease in PSS with CD5789 Cream B (-47.3±40.7%) than with Vehicle (-5.4±25.0%). The difference between study treatments was -41.9±43.6% (p<0.001), which was considered clinically significant.

When considering each CD5789 concentration separately, there was trend for a greater decrease in IGA with Active Treatment than Vehicle; the difference between study treatments was -1.2±2.4 points with 100 µg/g and -0.9±2.4 point CD5789 with 50 µg/g. A similar trend was found for TSS. For each CD5789 concentration, there was a statistically significantly greater decrease in PSS, scaling and roughness with Active Treatment than Vehicle (p<0.05). There was no effect of CD5789 Cream B on erythema at either 100 µg/g or 50 µg/g.

At the end of treatment, the comparison of the 2 target zones revealed that CD5789 Cream B was considered better than its Vehicle by the Investigator and the patient in 65.4% and 73.1% of cases, respectively (evaluation of "better" or "much better" on the 4-point scale). Similar results were found with each CD5789 concentration. CD5789 100 µg/g Cream B was considered better than its Vehicle by the Investigator and the patient in 61.5% and 69.2% of cases, respectively, while CD5789 50 µg/g Cream B was considered better than its Vehicle by the Investigator and the patient in 69.2% and 76.9% of cases.

Success in response to treatment, defined as meeting the following 3 conditions at the end of treatment (scaling =0 or 1, change in scaling from Baseline ≥2 and roughness =0 or 1), was found in 53.8% and 23.1% of patients with the 100 µg/g and the 50 µg/g concentration of CD5789, respectively.

Similar efficacy results were found in the ITT population.

Sub-group analyses per type of ichthyosis

In patients with LI (N=17), IGA decreased by 2.0±2.3 points with Active Treatment, whereas it remained stable with Vehicle (-0.1±1.4 point). The difference between Active Treatment and Vehicle was 1.9±1.5 points on a scale of 10, which was statistically significant (p<0.001). CD5789 Cream B also decreased TSS, PSS, scaling and roughness (p<0.01) but had no effect on erythema. The difference between study treatments regarding the decrease in PSS over 6 weeks was -41.3±38.1% (p=0.002) and was similar for each CD5789 concentration. At the end of treatment, CD5789 Cream B was

	considered better than its Vehicle by the Investigator and the patient with LI in 76.5% and 88.2% of cases. In patients with RXLI (N=9), IGA decreased by 1.2±1.9 points with Active Treatment and 1.8±1.6 points with Vehicle (no difference between study treatments). There was a trend for a greater decrease of TSS, PSS, scaling and roughness with Active Treatment than Vehicle. In contrast, the erythema score increased with CD5789 Cream B whereas it decreased with Vehicle. The difference between study treatments regarding the decrease in PSS was -43.0±55.1% ($p>0.05$; statistical significance was attained in the ITT population, $p=0.039$). At the end of treatment, CD5789 Cream B was considered better than its Vehicle by the Investigator and the patient with RXLI in 44.4% of cases. Similar efficacy results were found in the ITT population.
21. Safety outcomes	Assessment of local cutaneous tolerance in the Safety population showed that Vehicle Cream B induced no or mild signs of irritation and stinging/burning. When pooling both types of ichthyosis, severe signs of irritation were reported as the worst score in a higher proportion of patients with CD5789 100 µg/g Cream B (4/17 patients, 23.5%) than with CD5789 50 µg/g Cream B (1/14 patients, 7.1%). Moderate signs of irritation were reported in 3 patients with each concentration (17.6% with 100 µg/g and 21.4% with 50 µg/g). There were no severe signs of stinging/burning in this study. Moderate signs of stinging/burning were only reported in 1/17 patients with CD5789 Cream B 100 µg/g (5.9%). Considering each type of ichthyosis separately,severe signs of irritation were reported as the worst score in a lower proportion of patients with LI (2/21 patients, 9.5%) than patients with RXLI (3/10 patients, 30.0%). In patients with LI, severe signs of irritation were reported with the 100 µg/g concentration (1/11 patient, 9.1%) and the 50 µg/g concentration (1/10 patient, 10.0%) whereas in patients with RXLI, they were all reported with CD5789 100 µg/g Cream B (3/6 patients, 50.0%). Moderate signs of stinging/burning were only reported in 1 patient with RXLI, on a target zone treated with CD5789 100 µg/g Cream B. An overview of treatment-emergent AEs (TEAEs) reported in the Safety population is presented Table 4 and treatment-related TEAEs are presented in Table 5.

Table 4 Overview of treatment-emergent adverse events - Safety population

	CD5789 100 µg/g (N= 17)			Vehicle (N= 17)			Overall (N= 17)		
	n events	n subj.	% subj.	n events	n subj.	% subj.	n events	n subj.	% subj.
All AEs	12	7	41.2	5	2	11.8	12	7	41.2
Related AEs to study drug	7	6	35.3	0	0	0.0	7	6	35.3
Related AEs to protocol procedure	0	0	0.0	0	0	0.0	0	0	0.0
Related AEs	7	6	35.3	0	0	0.0	7	6	35.3
All cutaneous AEs	7	6	35.3	0	0	0.0	7	6	35.3
Related cutaneous AEs	7	6	35.3	0	0	0.0	7	6	35.3
Non cutaneous AEs	5	2	11.8	5	2	11.8	5	2	11.8
Related non cutaneous AEs	0	0	0.0	0	0	0.0	0	0	0.0
All serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
All AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
AESIs	6	5	29.4	0	0	0.0	6	5	29.4
Related AESIs	6	5	29.4	0	0	0.0	6	5	29.4
Deaths	0	0	0.0	0	0	0.0	0	0	0.0
	CD5789 50 µg/g (N= 14)			Vehicle (N= 14)			Overall (N= 14)		
	n events	n subj.	% subj.	n events	n subj.	% subj.	n events	n subj.	% subj.
All AEs	9	6	42.9	9	6	42.9	9	6	42.9
Related AEs to study drug	1	1	7.1	1	1	7.1	1	1	7.1
Related AEs to protocol procedure	0	0	0.0	0	0	0.0	0	0	0.0
Related AEs	1	1	7.1	1	1	7.1	1	1	7.1
All cutaneous AEs	2	2	14.3	2	2	14.3	2	2	14.3
Related cutaneous AEs	1	1	7.1	1	1	7.1	1	1	7.1
Non cutaneous AEs	7	4	28.6	7	4	28.6	7	4	28.6
Related non cutaneous AEs	0	0	0.0	0	0	0.0	0	0	0.0
All serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
All AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
AESIs	0	0	0.0	0	0	0.0	0	0	0.0
Related AESIs	0	0	0.0	0	0	0.0	0	0	0.0
Deaths	0	0	0.0	0	0	0.0	0	0	0.0
	CD5789 in overall (N= 31)			Vehicle (N= 31)			Overall (N= 31)		
	n events	n subj.	% subj.	n events	n subj.	% subj.	n events	n subj.	% subj.
All AEs	21	13	41.9	14	8	25.8	21	13	41.9
Related AEs to study drug	8	7	22.6	1	1	3.2	8	7	22.6
Related AEs to protocol procedure	0	0	0.0	0	0	0.0	0	0	0.0
Related AEs	8	7	22.6	1	1	3.2	8	7	22.6
All cutaneous AEs	9	8	25.8	2	2	6.5	9	8	25.8
Related cutaneous AEs	8	7	22.6	1	1	3.2	8	7	22.6
Non cutaneous AEs	12	6	19.4	12	6	19.4	12	6	19.4
Related non cutaneous AEs	0	0	0.0	0	0	0.0	0	0	0.0
All serious AEs	0	0	0.0	0	0	0.0	0	0	0.0
All AEs leading to discontinuation	0	0	0.0	0	0	0.0	0	0	0.0
AESIs	6	5	16.1	0	0	0.0	6	5	16.1
Related AESIs	6	5	16.1	0	0	0.0	6	5	16.1
Deaths	0	0	0.0	0	0	0.0	0	0	0.0

AEs were summarized only for events that occurred after the first use of medication.
Related AEs were AEs related to a study drug and/or AEs related to a protocol procedure.
Cutaneous AEs comprise all AEs from the system organ class (SOC) Skin and Subcutaneous Tissue Disorders and one AE (oral herpes) from the SOC Infections and Infestations.
In the tables from Section 14.3, cutaneous AEs are reported as dermatologic AEs.
AESI: adverse event of special interest.
Overall includes CD5789 100 µg/g Cream B and CD5789 50 µg/g Cream B.
If an AE was not zone-specific, it was summarized in both target zones (Active Treatment and Vehicle).
The numbers in the columns cannot be added because a given subject could report more than 1 AE.

Table 5 Treatment-related adverse events - Safety population

		CD5789 100 µg/g vs. Vehicle		
		CD5789 100 µg/g (N=17)	Vehicle (N=17)	Overall (N=17)
MedDRA v14.0				
TOTAL NUMBER OF RELATED AEs		7	0	7
TOTAL NUMBER (%) OF SUBJECTS WITH RELATED AEs		6 (35.3%)		6 (35.3%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ALL	6 (35.3%)		6 (35.3%)
	ERYTHEMA	2 (11.8%)		2 (11.8%)
	PAIN OF SKIN	1 (5.9%)		1 (5.9%)
	SKIN BURNING SENSATION	1 (5.9%)		1 (5.9%)
	SKIN IRRITATION	3 (17.6%)		3 (17.6%)
		CD5789 50 µg/g vs. Vehicle		
		CD5789 50 µg/g (N=14)	Vehicle (N=14)	Overall (N=14)
MedDRA v14.0				
TOTAL NUMBER OF RELATED AEs		1	1	1
TOTAL NUMBER (%) OF SUBJECTS WITH RELATED AEs		1 (7.1%)	1 (7.1%)	1 (7.1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ALL	1 (7.1%)	1 (7.1%)	1 (7.1%)
	DERMATITIS ALLERGIC	1 (7.1%)	1 (7.1%)	1 (7.1%)
		CD5789 in overall vs. Vehicle		
		CD5789 in overall (N=31)	Vehicle (N=31)	Overall (N=31)
MedDRA v14.0				
TOTAL NUMBER OF RELATED AEs		8	1	8
TOTAL NUMBER (%) OF SUBJECTS WITH RELATED AEs		7 (22.6%)	1 (3.2%)	7 (22.6%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ALL	7 (22.6%)	1 (3.2%)	7 (22.6%)
	DERMATITIS ALLERGIC	1 (3.2%)	1 (3.2%)	1 (3.2%)
	ERYTHEMA	2 (6.5%)		2 (6.5%)
	PAIN OF SKIN	1 (3.2%)		1 (3.2%)
	SKIN BURNING SENSATION	1 (3.2%)		1 (3.2%)
	SKIN IRRITATION	3 (9.7%)		3 (9.7%)

A patient was counted once per system organ class (SOC) and once per preferred term (PT) even if more than one occurrence of an event was reported within a SOC or PT.

If an AE was not zone-specific, it was summarized in both target zones (Active Treatment and Vehicle).

The numbers in the columns cannot be added because a given subject could report more than 1 AE.

When pooling both CD5789 concentrations and both types of ichthyosis, 21 TEAEs were reported in 13/31 patients (41.9%). All the TEAEs were of mild or moderate severity.

The proportion of patients who experienced TEAEs was similar with both concentrations of CD5789 Cream B: 12 TEAEs were reported in 7/17 patients (41.2%) with 100 µg/g (vs. 5 TEAEs in 2 patients, 11.8%, with the Vehicle) and 9 TEAEs were reported in 6/14 patients (42.9%) with 50 µg/g (vs. 9 TEAEs in 6 patients, 42.9%, with the Vehicle).

The most frequently reported TEAEs were cutaneous TEAEs (9 events in 8/31 patients), 8 events were in the SOC Skin and Subcutaneous Tissue Disorders and one event (oral herpes) was in the SOC Infections and Infestations. Eight out of these 9 events were considered by the Investigator to be related to treatment. There were no other treatment-related TEAEs. The proportion of patients who reported treatment-related cutaneous TEAEs was higher with the 100 µg/g concentration of CD5789 (6/17 patients, 35.3%) than with the 50 µg/g concentration of CD5789 (1/14 patients, 7.1%).

The treatment-related cutaneous TEAEs reported with CD5789 100 µg/g Cream B were: skin irritation (3 patients, 17.6%) -the most frequently reported TEAE-, erythema (2 patients, 11.8%), pain of skin and skin burning sensation (each in 1 patient, 5.9%). Only 1 cutaneous event (dermatitis allergic) was reported with CD5789 50 µg/g Cream B and

	the Vehicle. The only noncutaneous TEAE reported in more than 1 patient was headache (2 patients, 6.5%), 1 patient with each CD5789 concentration. There were 6 AEs of special interest (AESIs) reported by 5/31 patients (16.1%). These AESIs were all cutaneous events related to the study drug CD5789 100 µg/g Cream B. Subgroup analyses per type of ichthyosis showed that the proportion of patients who reported TEAEs was slightly lower in patients with LI (14 events in 8/21 patients, 38.1%) than in patients with RXLI (7 events in 5/10 patients, 50.0%). A greater proportion of patients with LI reported treatment-related cutaneous TEAEs with the 100 µg/g concentration (3/11 patients, 27.3%) than the 50 µg/g concentration of CD5789 Cream B (1/10 patients, 10.0%). Similar results were found in patients with RXLI, with treatment-related cutaneous TEAEs being reported in 3/6 patients with 100 µg/g (50.0%) and 0/4 patients with 50 µg/g (0%). A greater proportion of patients with LI reported treatment-related cutaneous TEAEs with the 100 µg/g concentration (3/11 patients, 27.3%) than the 50 µg/g concentration of CD5789 Cream B (1/10 patients, 10.0%). Similar results were found in patients with RXLI, with treatment-related cutaneous TEAEs being reported in 3/6 patients with 100 µg/g (50.0%) and 0/4 patients with 50 µg/g (0%). There were no serious AEs (SAEs), no TEAEs leading to discontinuation and no deaths in this study. No safety concerns were raised by assessment of laboratory safety tests, vital signs (and ECG in the USA) or physical examination.
22. Summary (conclusion)	From these data, it can be concluded that CD5789 Cream B at a concentration of 100 µg/g or 50 µg/g is effective in decreasing scaling and roughness in patients with LI. The treatment was well tolerated in these patients, with acceptable signs of irritation. In patients with RXLI, there was a trend for positive effects of CD5789 Cream B on scaling and roughness. However, the sample size was too small to reach a valid conclusion. In addition, in patients with RXLI, irritation was not acceptable for CD5789 at a concentration of 100 µg/g.

Applicant (Marketing Authorization Holder)	(signature) Régis Schulz (full name) GALDERMA SA Zählerweg 10 CH-6300 Zug 058 455 85 00

Annex 30
to the Procedure for expertise of registration materials for medicinal products submitted for state registration (renewal), as well as expertise of the materials on variations to the registration materials during the marketing authorization validity period
(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
3. Manufacturer	**LABORATOIRES GALDERMA** **ZI Montdesir** **74540 ALBY-SUR-CHERAN** **France**
4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	Exploratory study to evaluate the safety and efficacy of CD5789 in subjects with early-stage cutaneous T-cell lymphoma, rd-03-spr-40201e
6. Clinical study phase	Phase 1
7. Clinical study period	Date of first subject screened: 4th April 2013 Date of last subject completed: 26th February 2014
8. Countries where clinical study was conducted	United States of America
9. Number of subjects	Ten (10) subjects were planned to be enrolled; a total of 10 subjects were included in the study, all were included in the intent-to-treat (ITT), per-protocol (PP) and Safety populations and all completed the study.

	Composite Assessment of Index Lesions Severity (CAILS) score for each index lesion. The CAILS score is a sum (0-50) of the scores of the index lesion size (scale from 0 [no measurable area] to 18 [>300 cm^2]) and severity (from 0 [none] to 8 [very severe/extreme], including the evaluation of erythema, scaling, plaque elevation, pigmentation abnormalities). The efficacy endpoints were: - Change in subject biopsy score. - CAILS score and percentage reduction in CAILS score at the end of the study. - Lesion response, defined as the number of lesions entirely cleared (CAILS score of 0).
17. Safety evaluation criteria	Safety was evaluated by: - Assessment of local tolerability using a 5-point scale. - Assessment of functional signs (pruritus, stinging/burning) using a 4-point scale. - Monitoring of AEs. - Physical examination and record of vital signs, laboratory safety tests, ECGs.
18. Statistical methods	Prior to analysis, the CAILS score recorded for each lesion was averaged across the index lesions (except the one for biopsy) of each subject. In addition, the CAILS score recorded for each lesion was summed across the index lesions (except the one for biopsy) of each subject. CAILS scores and their percent changes from Baseline were summarized using means, medians, minimums, maximums, and standard deviations (SDs) for the data collected at each visit. Individual signs and lesion size part of the CAILS score was summarized in the same way as the CAILS score, but no percent was calculated. Graphs of mean values over time were generated. Lesion response, i.e., the proportion of lesions with a CAILS score of zero was summarized, after pooling all lesions from all subjects. The averaged CAILS score across lesions of each subject was compared between before treatment and at each subsequent visit using the two-sided Wilcoxon rank signed test. Significance was assessed at the 0.10 level. Comparisons with previous visits were interpreted conditionally on the significance of later visits. Percent changes from Baseline in CAILS scores were analyzed in the same way. Individual signs and lesion size part of CAILS scores were analyzed using the same method as for CAILS scores.
19. Demographic indicators of the study population (gender, age, race, etc.)	Most subjects were white (70%) with a mean age±SD of 57.9±14.5 years, and there were more male (60%) than female subjects. At Baseline, subjects had between 2 and 6 stable lesions, with a combined surface area of <6000 cm^2. The mean CAILS score±SD per lesion was 11.93±3.47 with a range of 8.0-17.7.
20. Efficacy outcomes	- Biopsy score Due to a minimal/no reduction in lymphocytic filtration on subjects' biopsies (slight reduction observed only in 2 subjects), the biopsy score by quantitative image analysis was not performed. - CAILS score There was no statistically significant change in CAILS score or percentage reduction in CAILS score between Baseline and Week 12/ET. Identical results were obtained whether the CAILS score was calculated based on average across lesions or on sum across lesions. For subjects' individual signs and lesion size, erythema increased in Week 2, scaling increased in Weeks 1 and 2 and plaque elevation decreased in Week 8. Pigmentation

	abnormalities increased in Weeks 8 and 12. Lesion size initially increased (Weeks 1 to 4) before decreasing towards the end of the study. - Lesion response Out of 45 lesions evaluated, 1 lesion (2.2%) reached a CAILS score of 0 at Week 12/ET.
21. Safety outcomes	Mean worst local tolerance remained initially constant over time, before decreasing towards the end of the study. The majority of subjects exhibited a minimal worst local tolerance score. Mean worst stinging/burning sensations and pruritus increased slightly at the beginning of the study, as was expected, before decreasing as the study progressed. Most subjects experienced at worst mild stinging/burning sensations and either no, or mild pruritus. No subjects experienced a worst score of severe in either of the assessments (local tolerability, functional signs). An overview of the AEs that occurred in subjects included in the Safety population is presented in the Table below. During the study, 5 subjects experienced 8 AEs. Of these, 6 were cutaneous AEs (4 subjects) of which 4 were considered related to treatment (3 subjects) and these accounted for all related AEs. No serious AEs, no deaths and no Adverse Events of Special Interest (AESIs) occurred during the study. No clinically significant changes in blood chemistry, hematology, virology, vital signs or ECGs were observed during this study. **Table 1 Overview of AEs**

	CD5789 (N= 10)		
	n events	n subjects	% subjects
All AEs	8	5	50.0
Related AEs to study drug	4	3	30.0
Related AEs to protocol procedure	0	0	0.0
Related* AEs	4	3	30.0
All cutaneous AEs	6	4	40.0
Related* cutaneous AEs	4	3	30.0
Non cutaneous AEs	2	2	20.0
Related* non cutaneous AEs	0	0	0.0
All serious AEs	0	0	0.0
Related* serious AEs	0	0	0.0
All AEs leading to discontinuation	0	0	0.0
Related* AEs leading to discontinuation	0	0	0.0
AESIs	0	0	0.0
Related* AESIs	0	0	0.0
Deaths	0	0	0.0

*Related AEs = related AEs to study drug and/or related to protocol procedure. Note: The numbers in the columns cannot be added because a given subject could report more than one AE.

22. Summary (conclusion)	In conclusion, CD5789 0.01% cream was well tolerated and safe when applied once daily for 12 weeks on patch or plaque early-stage (IA-IIA) CTCL. However, initial efficacy evaluations indicate that it is not effective in the treatment of early-stage (IA-IIA) CTCL.
Applicant (Marketing Authorization Holder)	(signature) Régis Schulz (full name) **GALDERMA SA** Zählerweg 10 CH-6300 Zug 058 455 85 00

Annex 30
to the Procedure for expertise of registration materials for medicinal products submitted for state registration (renewal), as well as expertise of the materials on variations to the registration materials during the marketing authorization validity period
(clause 4 of Section IV)

Report on Clinical Studies

1. Name of the medicinal product (marketing authorization number, if available)	**AKLIEF cream 0,005 %**
2. Applicant	**Galderma SA**
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4. Studies conducted:	☒ yes ☐ no if no, to justify
1) type of medicinal product for which the registration was conducted or planned	**Medicinal product with complete dossier**
5. Full name of clinical study, code number of clinical study	RD-03-SPR-40204E - Exploratory study to evaluate the safety and efficacy of CD5789 alone and in association with CD1680 in subjects with psoriasis.
6. Clinical study phase	Phase 1
7. Clinical study period	Date of first subject screened: 14 February 2013 Date of last subject completed: 27 June 2013
8. Countries where clinical study was conducted	Canada – France
9. Number of subjects	A total of 40 subjects were screened, 32 were randomized and included in the intent-to-treat (ITT) and safety populations. The per-protocol (PP) population comprised 29 subjects as 3 subjects were excluded due to major protocol deviations. One subject

<table>
<tr><td></td><td>Local tolerance was assessed at each application visit from Day 2, adverse events (AEs) were recorded along with physical examinations, vital signs and laboratory safety tests. Individual clinical scores and clearing scores were assessed twice weekly. At Day 25, tape-stripping and skin biopsies were performed, and D-Squames® were collected.</td></tr>
<tr><td>12. Main inclusion criteria</td><td>The study population comprised male and female subjects, aged 18 to 70 years, with a clinical diagnosis of stable plaque psoriasis, defined as no flare in the month before the Screening visit and Baseline visit.

At Baseline, each subject had 8 target sites (mini-zone of approximately 3 cm²) on one or more psoriatic plaques. All plaques presented similar severity (identical baseline total sum score [TSS; sum of individual scores of erythema, scaling and plaque elevation/induration] or variation of ±1 grade) with a TSS superior or equal to 6 and an individual score ±2.</td></tr>
<tr><td>13. Investigational medicinal product, method of administration, strength</td><td>▪ Test product dosage form
<table>
<tr><th></th><th colspan="6">Investigational product</th><th colspan="3">Comparator Product</th></tr>
<tr><th>Trade Name or Equivalent</th><th>CD5789 0.04% Cream (HE1 Concept)</th><th>CD5789 0.02% Cream (HE1 Concept)</th><th>CD5789 0.01% Cream (HE1 Concept)</th><th>CD5789 0.04% Cream (HE1 Concept) + Diprosone® 0.05% cream</th><th>CD5789 0.02% Cream (HE1 Concept) + Diprosone® 0.05% cream</th><th>CD5789 0.01% Cream (HE1 Concept) + Diprosone® 0.05% cream</th><th>CD5789 Cream Placebo</th><th>Diprosone® 0.05% cream</th><th>Dovobet® Ointment</th></tr>
<tr><td>Name of Drug Substance</td><td>NA</td><td>NA</td><td>NA</td><td>NA + Betamethasone dipropionate</td><td>NA + Betamethasone dipropionate</td><td>NA + Betamethasone dipropionate</td><td>NA</td><td>Betamethasone dipropionate</td><td>Calcipotriol - betamethasone dipropionate</td></tr>
<tr><td>Internal Code</td><td>CD5789</td><td>CD5789</td><td>CD5789</td><td>CD5789 + CD1680</td><td>CD5789 + CD1680</td><td>CD5789 + CD1680</td><td>NA</td><td>CD1680</td><td>NA</td></tr>
<tr><td>Pharmaceutical Form</td><td colspan="3">Cream</td><td colspan="3">Cream + Cream</td><td>Cream</td><td>Cream</td><td>Ointment</td></tr>
<tr><td>Concentration</td><td>400 µg/g</td><td>200 µg/g</td><td>100 µg/g</td><td>400 µg/g + 0.05%</td><td>200 µg/g+ 0.05%</td><td>100 µg/g+ 0.05%</td><td>NA</td><td>0.05%</td><td>50 µg/g – 500 µg/g</td></tr>
<tr><td>Formula Number</td><td>0298.0113</td><td>0298.0115</td><td>0298.0104</td><td>0298.0113 + NA</td><td>0298.0115 + NA</td><td>0298.0104 + NA</td><td>0298.0104P</td><td>NA</td><td>NA</td></tr>
<tr><td>Packaging (type and size)</td><td colspan="3">30 ml Amber glass bottle</td><td colspan="3">30 ml Amber glass bottle + 50 g tube</td><td>30 ml Amber glass bottle</td><td>50 g tube</td><td>60 g tube</td></tr>
<tr><td>Storage conditions</td><td colspan="3">Store below 25°C – Do not refrigerate and do not freeze</td><td colspan="3">Store below 25°C – Do not refrigerate and do not freeze + Store below 30°C – Do not freeze</td><td>Store below 25°C – Do not refrigerate and Do not freeze</td><td>Store below 30°C – Do not freeze</td><td>Store below 25°C - Do not freeze.</td></tr>
<tr><td>Dosage (total daily dose)</td><td colspan="3">50 µL</td><td colspan="3">50 µL + 50 µL</td><td>50 µL</td><td>50 µL</td><td>50 µL</td></tr>
<tr><td>Route</td><td colspan="9">topical</td></tr>
<tr><td>Dose Regimen</td><td colspan="9">Once daily</td></tr>
<tr><td>Duration of administration</td><td colspan="9">24 days (18 applications)</td></tr>
<tr><td>Location of Treated Area</td><td colspan="9">Mini-zones of 3 cm²</td></tr>
</table>
The more restrictive storage condition, which is "Store below 25°C, do not refrigerate and do not freeze", will be reported on the labels of each product.</td></tr>
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<tr><td>Name of Drug Substance</td><td>NA</td><td>NA</td><td>NA</td><td>NA + Betamethasone dipropionate</td><td>NA + Betamethasone dipropionate</td><td>NA + Betamethasone dipropionate</td><td>NA</td><td>Betamethasone dipropionate</td><td>Calcipotriol - betamethasone dipropionate</td></tr>
<tr><td>Internal Code</td><td>CD5789</td><td>CD5789</td><td>CD5789</td><td>CD5789 + CD1680</td><td>CD5789 + CD1680</td><td>CD5789 + CD1680</td><td>NA</td><td>CD1680</td><td>NA</td></tr>
<tr><td>Pharmaceutical Form</td><td colspan="3">Cream</td><td colspan="3">Cream + Cream</td><td>Cream</td><td>Cream</td><td>Ointment</td></tr>
<tr><td>Concentration</td><td>400 µg/g</td><td>200 µg/g</td><td>100 µg/g</td><td>400 µg/g + 0.05%</td><td>200 µg/g+ 0.05%</td><td>100 µg/g+ 0.05%</td><td>NA</td><td>0.05%</td><td>50 µg/g – 500 µg/g</td></tr>
<tr><td>Formula Number</td><td>0298.0113</td><td>0298.0115</td><td>0298.0104</td><td>0298.0113 + NA</td><td>0298.0115 + NA</td><td>0298.0104 + NA</td><td>0298.0104P</td><td>NA</td><td>NA</td></tr>
<tr><td>Packaging (type and size)</td><td colspan="3">30 ml Amber glass bottle</td><td colspan="3">30 ml Amber glass bottle + 50 g tube</td><td>30 ml Amber glass bottle</td><td>50 g tube</td><td>60 g tube</td></tr>
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<tr><td>15. Concomitant therapy</td><td>Not Applicable</td></tr>
</table>